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ANAESTHESIA AND PAIN MANAGEMENT FOR USE IN ORTHOPAEDIC DAY SURGERY

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*Don't part with your illusions. When
they are gone you may still exist, but
you have ceased to live.*

- Mark Twain

ABSTRACT

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ANAESTHESIA AND PAIN MANAGEMENT FOR USE IN ORTHOPAEDIC DAY SURGERY

From the Department of Anaesthesiology and Intensive Care, University of Turku, and the Division of Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital, Turku, Finland

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Day surgery has gained a large popularity during the last decades. In Finland, 57% of the elective procedures, and 50% at Turku University Hospital, were already conducted on day basis during 2012.

The steady growth of day surgery is mostly due to an increased safety in perioperative care and cost-effectiveness. The development of surgical techniques and anaesthetic methods has advanced the modern day surgery and extended the repertory of the procedures for use in day surgery operations. Day surgery also offers certain benefits like reduced risk for hospital-related infections, stress and confusion.

Patient satisfaction, regarding several issues, is high. Most concerns and complaints are related to postoperative pain, nausea and vomiting pain and nausea. Pain can hamper recovery and pain management is a crucial factor for hospital discharge. Appropriate pain treatment is effective, safe, easy and economical. A procedure-specific approach and an individually planned, multimodal analgesia should be the basis of modern pain management.

The main aim of this thesis was to evaluate the effectiveness and safety of anaesthetic technique and methods in pain treatment of orthopaedic day case surgery, and following conclusions were made. Unilateral spinal block was achieved using hyperbaric bupivacaine with a small dose of clonidine but clonidine prolonged the block. Continuous subacromial bupivacaine was found to be safe but conferring only moderate efficacy in pain care after shoulder arthroscopy. Transdermal fentanyl, 12 µg/h, as part of multimodal analgesia, offered a safe and easy option to pain management in this patient group. However, after forefoot surgery, it did not reduce pain any further. In general, pain scores in all patient groups were low and the need for rescue opioid moderate.

Keywords: pain management, multimodal analgesia, day surgery

TIIVISTELMÄ

Riika Merivirta

ORTOPEDISEN PÄIVÄKIRURGISEN POTILAAN ANESTESIA JA KIVUNHOITO

Anestesiologian ja tehohoidon oppiaine, Turun Yliopisto, ja
Toimenpide-, teho- ja kivunhoitopalvelujen palvelualue, Turun yliopistollinen
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Päiväkirurgian suosio on kasvanut viime vuosikymmeninä. Jo 57 % elektiivisistä leikkauksista Suomessa on päiväkirurgisia. Turun yliopistollisessa keskussairaalassa vastaava osuus on 50 %.

Päiväkirurgian jatkuva kasvu johtuu ennen kaikkea lisääntyneestä perioperatiivisen hoidon turvallisuudesta ja kustannustehokkuudesta. Kirurgisten tekniikoiden ja anestesia-menetelmien kehitys on mahdollistanut nykyaikaisen päiväkirurgian ja laajentanut päiväkirurgisena tehtävien toimenpiteiden valikoimaa. Päiväkirurgialla saavutetaan myös tiettyjä hyötyjä, kuten sairaalainfektioriskin, stressin ja sekavuuden vähenemistä.

Päiväkirurgiset potilaat ovat yleisesti ottaen erittäin tyytyväisiä; suurimpana huolen- ja palautteenannon aiheena ovat kipu ja pahoinvointi. Kipu voi haitata toipumista, ja kivunhoito onkin keskeinen tekijä kotiutuksen onnistumisessa. Hyvä kivunhoito on yksilöllisesti suunniteltua, tehokasta, turvallista, helppokäyttöistä ja taloudellista. Nykyaikaisessa päiväkirurgiassa hyödynnetään tyypillisesti multimodaalista eli useita eri kivunlievitysmenetelmiä käyttävää kivunhoitoa.

Tämän työn tarkoituksena oli selvittää tiettyjen kivunhoitomenetelmien tehoa ja turvallisuutta ortopedisillä päiväkirurgisilla potilailla. Hyperbarisen ja pieniannoksisen klonidiinin yhdistelmällä saavutettiin toispuoleinen puudutus, mutta klonidiini pidensi puutumusta. Subakromiaalisesti eli olkalisäkkeen alaiseen tilaan annettu bupivakaiini-infuusio osoittautui turvalliseksi, mutta sen hyöty olkapäätaahystyksen jälkeisessä kivunhoidossa oli vähäistä. Fentanylä 12 µg/h vapauttava laastari osana multimodaalista kivunhoitoa tarjosi turvallisen ja helpon vaihtoehdon olkapäätaahystyksen jälkeen. Jalkateräleikkauksen jälkeen se ei kuitenkaan vähentänyt kipua. Yleisesti ottaen kivun intensiteetti kaikissa tutkimusryhmissä oli matala ja tarve lisäopioidilääkitykselle vähäistä.

Avainsanat: kivunhoito, multimodaalinen kivunhoito, päiväkirurgia

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ABBREVIATIONS

AAG	α_1 -acid glycoprotein
ASA	the American Society of Anesthesiologists
BMI	body mass index
CNS	central nervous system
COMT	catechol- <i>O</i> -methyltransferase
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CYP	cytochrome P450
DBB	desbutylbupivacaine
ECG	electrocardiogram
HRQoL	health-related quality of life
<i>iv</i>	intravenous
MCID	minimal clinically important difference
MEC	minimal effective concentration
MTP	metatarsophalangeal
MUMM	Managed Update of Medical Methods
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
OHB	hydroxybupivacaine
OI	overall incidence
OSA	obstructive sleep apnoea
PACU	post anaesthesia care unit
PCA	patient controlled analgesia
PCS	pain catastrophizing scores
PDNV	postdischarge nausea and vomiting
<i>po</i>	peroral
PONV	postoperative nausea and vomiting
POD	postoperative day
SD	standard deviation
SpO ₂	peripheral arteriolar oxygen saturation
THL	National Institute for Health and Welfare
TIVA	total intravenous anaesthesia
VAS	visual analogue scale

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-V.

- I Merivirta R, Kuusniemi K, Jaakkola P, Pihlajamäki K, Pitkänen M. Unilateral spinal anaesthesia for outpatient surgery: a comparison between hyperbaric bupivacaine and bupivacaine–clonidine combination. *Acta Anaesthesiol Scand* 2009; 53: 788–793.
- II Merivirta RM, Kuusniemi KS, Hurme SA, Neuvonen PJ, Rautakorpi PJ, Olkkola KT, Leino KA. Plasma levels of bupivacaine and its metabolites after subacromial infusions in concentrations 2.5 or 5.0 mg/ml. *Acta Anaesthesiol Scand* 2011; 55: 228-233.
- III Merivirta R, Kuusniemi KS, Aantaa R, Hurme SA, Äärimaa V, Leino KA. The analgesic effect of continuous subacromial bupivacaine infusion after arthroscopic shoulder surgery: a randomized controlled trial. *Acta Anaesthesiol Scand* 2012; 56: 210-216.
- IV Merivirta R, Äärimaa V, Aantaa R, Koivisto M, Leino K, Liukas A, Kuusniemi K. Postoperative fentanyl patch vs. subacromial bupivacaine infusion in arthroscopic shoulder surgery. *Arthroscopy* 2013; 29: 1129-1134.
- V Merivirta R, Pitkänen M, Alanen J, Haapoja E, Koivisto M, Kuusniemi K. Postoperative pain management with transdermal fentanyl after forefoot surgery: a randomized placebo controlled study. Submitted for publication.

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1. INTRODUCTION

Musculoskeletal disorders constitute a major health problem in Finland, and occur in approximately one-fifth of the Finnish population, aged 30-64 years in employment and one-third of those outside the workforce suffering from these problems (National Public Health Institute, Taimela et al 2007). One-third of both sickness benefits and new disability pensions (recipients, aged 16-65 and resident in Finland) compensated by the Social Insurance Institution of Finland were caused by musculoskeletal disorders during 2012 (Kela) and this lead to significant societal costs. Lower back and neck pain are the most reported musculoskeletal problems (THL, Report 68/2012). Twenty-six % of women and 29 % of men report pain in the shoulder, and 33 % and 29 %, women and men, respectively, reported pain in the knee.

There were 426 000 periods of care needing surgical procedures in Finland during 2012 (SOTKAnet 2013). The most common procedure involved musculoskeletal disorders, which caused 21 % (over 133 000) of periods of care (THL/SVT, Fredriksson et al 2013). During 2011, procedures for knee and tibia were the second largest group among all procedures (THL/SVT, Rautiainen et al 2012). If only procedures for musculoskeletal disorders were evaluated, procedures for knee and tibia consisted of the largest group comprising of almost 40 000 patients, procedures for shoulder, clavicle and scapula were second with 20 000 patients, and ankle and forefoot operations were third with 19 000 patients during 2011 (THL/SVT, Rautiainen et al. 2012). Fifty-seven percent of elective surgery was day surgery, i.e., patients were admitted and discharged on the same day (THL/SVT, Rautiainen et al. 2012). The popularity of day surgery has increased by 13-percentage units in twelve years though there are still wide variations in hospitals.

As postoperative pain, nausea and vomiting are the most frequently reported symptoms and causes for admission after day surgery (Chung et al. 1996, Wu et al. 2002, Mattila et al. 2005) postoperative pain and antiemetic management are crucial for successful discharge. Multimodal analgesia, a combination of different analgesics acting by different mechanisms, is the current standard of care. It does not only improve analgesia but it reduces the incidence of adverse effects and may shorten the hospital stay. Multimodal analgesia typically consists of opioids combined with nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 (NSAIDs/COX-2) inhibitors, paracetamol, glucocorticoids and antiepileptics but also different analgesic techniques, such as local anaesthetic infiltration or nerve blocks, can be combined with them (Kehlet et al. 1993, Elvir-Lazo et al. 2010).

The most commonly used analgesics, both pre- and postoperatively, are NSAIDs and paracetamol, which are often combined with opioids, codeine and tramadol, in the postoperative phase (Segerdahl et al. 2008). Also, glucocorticoids reduce the need for opioid, even after single dose administration (Bisgaard et al .2003, Murphy et al. 2011). Local anaesthetics can be used for perineural blocks, wound infiltrations or infusions. They are also used for central neuraxial anaesthesia with or without adjuncts with the intention to intensify and/or prolong the effect of local anaesthetic. One of

these adjuvants is clonidine, an α_2 -agonist, which can be administered, e.g., intrathecally and epidurally. Multimodal analgesia reduces the need for opioids.

Orthopaedic surgery outpatients experience moderate to severe pain postoperatively in the postanesthesia unit and also still at home (Chung et al. 1996, Rawal et al. 1997). The administration routes of opioids are many with the peroral (*po*) route being the most simple and intramuscular or subcutaneous route being the most uncomfortable. Intravenous (*iv*) infusions or patient controlled analgesia (PCA-) technique are not suitable for day surgery but transdermal opioids, as fentanyl, are able to offer continuous pain relief without a need for intravenous access. A notable matter is also compliance of the patients, which affects the success of pain care. Many of the patients follow the given instructions concerning pain management at home independently. As the complexity for the instructions or the pain relief technique increases, the probability for failure in pain care treatment also rises.

The series of these studies scrutinizes the effectiveness and safety of different possible alternatives for use in orthopaedic outpatients' pain care. The majority of orthopaedic day surgery operations consisted of knee and shoulder arthroscopies and therefore pain treatment in these operations was studied. These studies were carried out to evaluate methods that would allow early discharge, would be effective and easy to use in order to ensure patient satisfaction and adherence, and would be cost-effective in this patient group.

2. REVIEW OF THE LITERATURE

2.1. Day Surgery

Day surgery can be defined as a practice of admitting selected patients into the hospital for elective surgery and discharging them on the same day (IIAS Day Surgery Handbook). The surgical procedures are carried out in operating rooms, and *iv*-sedation, general anaesthesia, or anaesthetic is required (IIAS 2007, Current Care Guidelines 2014). Nowadays, day surgery can be considered as the norm for all elective surgery.

2.1.1. History

As there is incisively written in the review of “History of anesthesia for ambulatory surgery”, earlier practitioners were considered ambulatory while patients stayed at home during surgical procedures (Urman et al. 2012). The situation changed when anaesthesia was developed and anaesthetic agents like ether and nitrous oxide found their place in the mid-19th century. The first anaesthesia with ether for surgery was performed as early as 1842, when James Venable underwent a removal of a mass on the neck. The roots of modern day surgery date back to the early twentieth century when James Nicoll’s study, “The surgery of infancy”, which advocated for outpatient surgery, was published (Nicoll 1909). Already as early as 1915, economical benefits were distinguished by a physician interested in anaesthesia, RM Waters, who was established a general administrative framework for ambulatory practice (Urman et al. 2012). For decades, the advancement was modest until 1969 when the first freestanding day surgery unit was based in USA (Reed et al. 1974). During the 1980s and 1990s, there was a dramatic increase in these units (Jarrett et al. 2006), and during the beginning of 1970s, day surgery began in Finland, with Helsinki and Kuopio being at the frontline (Lahtinen et al. 1998).

Over the last two decades, there has been substantial growth of day surgery, from 5 % in 1990 to 57 % in 2012, in Finland (THL/SVT, Fredriksson et al. 2013), but still not growing as fast as was expected (Lahtinen et al 1998). However, the percentages vary considerably between the hospitals and, in 2010, the range was between 48-65 % (34 % in Ahvenanmaa) (THL/SVT, Fredriksson et al. 2013). More than half of operations (54 %) in the Southwest Finland Hospital District in 2012 were performed on a day basis. Increasing the number of outpatients and developing the preoperative evaluation can be regarded as future challenges.

Table 1. Total and *in-per-capita* number of elective periods of care and proportion of day surgical procedures by hospital district, 2000-2011 (modified from the table of THL/SVT, Rautiainen et al. 2012).

Hospital district	2000		2005		2010		2011	
	Care periods nr	Day surgery %	Care periods nr	Day surgery %	Care periods nr	Day surgery %	Care periods nr	Day surgery %
WHOLE COUNTRY	341 975	44	360 914	51	348 987	56	354 789	57
Ahvenanmaa	1 660	29	1 708	32	1 590		1 628	37
Helsinki and Uusimaa Hospital District	85 195	37	91 185	52	89 970	58	90 231	59
South Karelia Hospital District	8 667	49	7 456	50	8 009	58	8 624	59
Kymenlaakso Hospital District	12 097	43	13 250	50	12 073	60	13 392	60
Southwest Finland Hospital District	37 448	40	37 950	50	35 585	56	35 756	57
Satakunta Hospital District	17 610	45	16 892	53	16 272	55	17 387	58
Pirkanmaa Hospital District	26 632	44	31 900	57	32 326	58	32 962	59
Vaasa Hospital District	8 732	38	10 099	51	10 804	54	10 817	56
South Ostrobothnia Hospital District	12 517	34	13 022	43	12 471	50	12 949	50
Kanta-Häme Hospital District	11 542	38	10 551	50	10 906	55	11 707	57
Päijät-Häme Hospital District	18 881	49	15 997	57	14 315	62	14 305	63
Pohjois-Savo Hospital District	18 585	40	21 027	50	17 267	46	16 952	45
Central Finland Hospital District	14 806	36	15 571	51	13 636	50	15 883	55
Etelä-Savo Hospital District	6 149	33	6 977	51	6 780	57	7 265	58
North Karelia Hospital District	10 784	33	11 304	42	11 355	51	11 755	51
Itä-Savo Hospital District	5 180	4	4 589	55	4 270	55	3 490	57
North Ostrobothnia Hospital District	26 577	36	27 408	51	28 082	57	26 596	61
Central Ostrobothnia Hospital District	5 952	1	5 209	55	5 047	55	4 864	57
Kainuu Hospital District	5 430	2	5 037	39	5 042	47	5 323	50
Lapland Hospital District	8 098	41	8 343	43	8 366	55	8 140	55
Länsi-Pohja Hospital District	5 053	41	5 026	50	4 821	53	4 763	54

2.1.2. Patients

Over the years, the patient selection criteria has changed. Earlier, only patients belonging to the ASA (American Society of Anesthesiologists) physical status I and II groups were considered suitable, but nowadays many ASA III patients are widely

accepted for outpatient surgery (Friedman et al. 2004). Almost 20 % of anaesthetists were willing to include also ASA IV patients (Friedman et al. 2004). Also an increasing number of elderly and higher risk patients have been accepted suitable for day surgery.

2.1.2.1. Morbidity and mortality in ambulatory surgical patients

According to a Danish multicentre study, major morbidity is rare in day surgery (Majholm et al. 2012). A recent American multicentre study showed that the incidence of mortality and morbidity, among adult patients within 72 hours postoperatively, is 0.1 % (Mathis et al. 2013). Clinical data was gathered prospectively from almost 245 000 patients undergoing general, plastic, orthopaedic, urologic, obstetric, gynaecologic and vascular surgical procedures in 250 centres across the USA. The most common morbidities were early postoperative pneumonia, unplanned postoperative intubation, wound disruption, and bleeding requiring blood transfusion. The investigators defined seven independent risk factors, which were being overweight and obese body mass index, chronic obstructive pulmonary disease (COPD), a history of transient ischemic attack/stroke, hypertension, previous cardiac surgical intervention, and prolonged operative time (Mathis et al. 2013). Already 15 years earlier, hypertension and obesity were noticed to be risk factors (Chung et al. 1999). Though obesity was an independent predictor for an unplanned admission in the fore mentioned study (Mathis et al. 2013), in another study, obesity did not increase the number of admissions, despite of the fact that obese patients had more episodes of bronchospasm and required supplemental oxygen more frequently (Hofer et al 2008). Also, elderly people (>65 years old) have an increased risk for intraoperative adverse events, which are mainly cardiovascular, compared with younger patients (Chung et al. 1999). Elderly people, however, are not a functionally or physiologically heterogeneous group. One describing term for physiological reserves is “frailty”, which is defined as a syndrome consisting of weight loss, exhaustion, slow walking speed, low activity and weakness (Fried et al. 2001). It predicts hospitalization and death among older adults (Fried et al. 2001) but also postoperative complications and hospital stay after surgery (Makary et al. 2010, Revenig et al. 2013). Both age and severe obesity increases the probability of comorbidities (Chung et al. 1999, Hofer et al. 2008) and obstructive sleep apnoea (OSA) related to obesity is one example. When evaluating severely obese patients for bariatric surgery, the incidence of OSA was as high as 88 % (Frey et al. 2003), while earlier the incidence among severely obese men has been reported to be 50 % and 3 % among women (Vgontzas et al. 1994). Though there are reports that OSA is not an independent risk factor and not associated with increased adverse effects during day surgery (Sabers et al. 2003, Liu et al. 2010), OSA patients’ eligibility for day surgery is controversial and many of the anaesthetist disagree to anaesthetise a patient on a day basis, if opioids or general anaesthesia are needed (Friedman et al. 2004). The consensus statement by the Society for Ambulatory Anesthesia (SAMBA) regard OSA patients eligible as outpatients, if their comorbidities are optimised and patients are able to use a continuous positive airway pressure device after discharge (Joshi et al. 2012). Pre-existing medical conditions of any patient can predict perioperative adverse effects (Chung et al. 1999, Mathis et al. 2013) and the operability of outpatients should

be evaluated using the same principals as for inpatients (Current Care Guidelines 2014).

2.1.3. Orthopaedic procedures

Twenty-one percent of all periods of care with procedures, in Finland during 2012 are caused by musculoskeletal disorders, and 45 % of them are performed on a day basis (THL/SVT Fredriksson et al. 2013). In Sweden, the proportion of orthopaedics, in day surgery, is 33 % (Segerdahl et al. 2008).

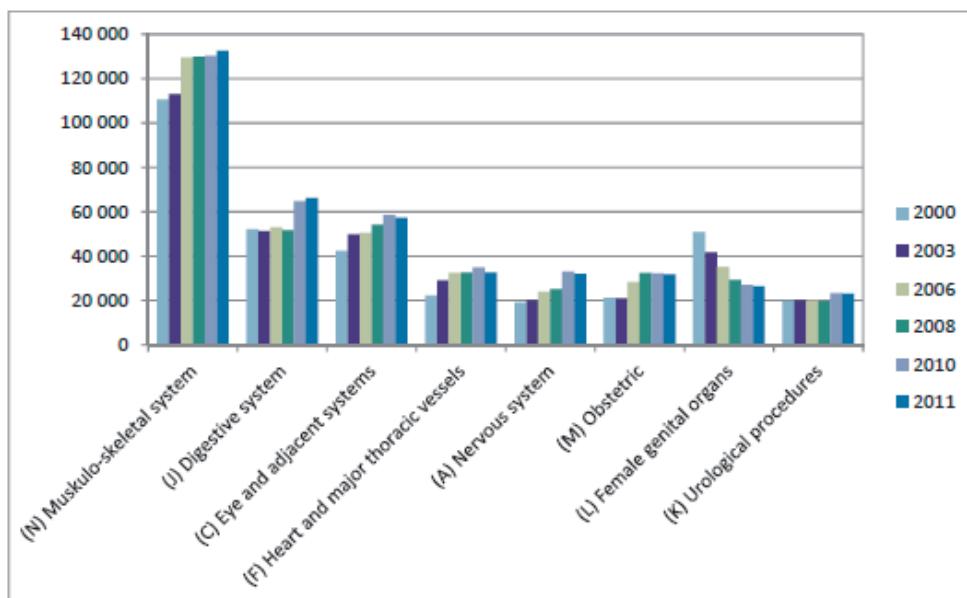


Figure 1. Most common single character code procedures measured by total number of periods of care, 2000-2011 (THL/SVT, Rautiainen et al. 2012).

2.1.3.1. Knee arthroscopy

Knee arthroscopy was the most frequently performed orthopaedic procedure and the second most common surgical procedure after cataract surgery during 2012. In Finland, 14 000 partial meniscectomies (NGD05) and debridements (NGF25) were operated during 2012 (THL/SVT, Fredriksson et al. 2013). At the Surgical Hospital of Turku University Hospital, over 800 knee arthroscopies were performed during 2007 with 721 of them for partial meniscectomies and debridement operations (Fig. 2). During year 2012, only 200 knee arthroscopies were performed. This change in surgical practise results from the findings that show that arthroscopic lavage or debridement does not provide any benefit for patients who have osteoarthritis (Moseley et al. 2002, Kirkley et al. 2008), or a partial meniscectomy for patients with degenerative meniscus tear or mild to moderate osteoarthritis (Sihvonen et al. 2013, Katz 2013).

Spinal anaesthesia seems to be the most used anaesthesia method for knee arthroscopy in Finland (Intensium Ltd.), as also at the Surgical Hospital, where a unilateral spinal block is the method of choice. One widely used method to achieve a unilateral spinal block with an intense motor block to a desired side with minimal hemodynamic changes is the use of a small dose of long-acting local anaesthetic and the restriction of the block at the operative side (Casati et al. 1998, Kuusniemi et al. 2000, Valanne et al. 2001). A unilateral block causes a more intense motor block and the reduction of the dose of local anaesthetic is possible. Another option to reduce a dose of local anaesthetics or intensify the block is to use adjuncts, like opioids or α_2 -agonists (Ben-David et al. 1997, DeKock et al. 2001, van Tuijl et al. 2008). There is a small increase in time to reach surgical block in unilateral block compared to conventional block (Casati et al. 1999, Fanelli et al. 2000), however, this 3 to 4 minutes difference is without clinical significance. The regression of both sensory and motor blocks with bupivacaine takes more time after unilateral block, probably because of more intensified and concentrated block (Casati et al. 1999, Fanelli et al. 2000).

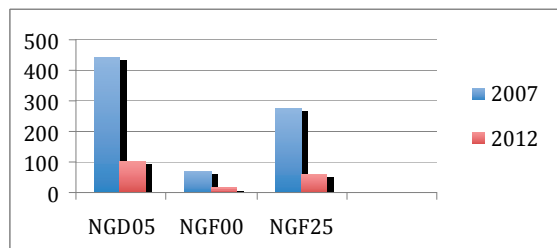


Figure 2. The number of partial meniscectomies (NGD05), excisions of plica of synovium of knee (NGF00) and arthroscopic debridements (NGF25) at Surgical Hospital during the years 2007 and 2012.

2.1.3.2. Shoulder arthroscopy

Shoulder arthroscopy is a common procedure with 7500 operations occurring during 2012 in Finland (THL/SVT, Fredriksson et al. 2013). Over 80% of them were performed on day basis. Depending on the procedure, this percentage grew from 10 to 20 % over two years. At the Surgical Hospital, 500 shoulder arthroscopies were performed during 2009 compared to 240, during 2012 (Fig. 3).

A similar change in surgical practice that concerned shoulder arthroscopies than knee arthroscopies caused a decrease in amount of operations performed. Finnish studies show that surgery is not superior to conservative treatment with physiotherapeutic exercise in impingement syndromes and rotator cuff tears (Ketola et al. 2009, Kukkonen et al. 2014) and this may explain this change.

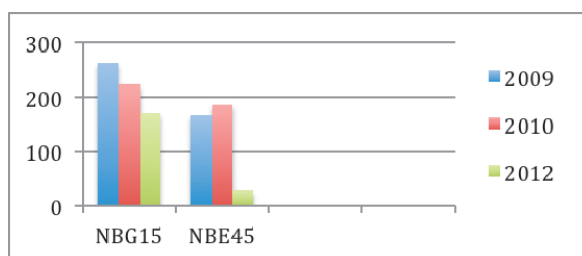


Figure 3. The numbers of arthroscopic acromionplasties (NBG15) and arthroscopic plastic repairs of ligament of shoulder (NBE45) at the Surgical Hospital during the years 2009, 2010 and 2012.

2.1.3.3. Forefoot surgery

The most performed forefoot surgery procedures for hallux valgus and rigidus are the fusion between the ankle and the foot, the fusion of the first metatarsal bone, an osteotomy of the first metatarsal bone and other operations of foot bones in Finland. The number of these procedures was approximately 5000 during 2012 (THL/SVT Fredriksson et al. 2013). Osteotomies of the first metatarsal bone (NHK30) and other operations of foot bones (NHK99) were performed in 70-74 % cases as day basis, and for fusions of the first metatarsal bone (NHG80) 60 % but fusions between the ankle and the foot (NHG26) were only 36 %. At the Surgical Hospital of Turku University Hospital a number of these procedures has increased by one-third, a total of 255 cases during 2012.

2.2. Pain and other postoperative and postdischarge symptoms after day surgery

2.2.1. Pain

Thirty to forty percent of outpatients have moderate to severe pain after surgery (Beauregard et al. 1998, McGrath et al. 2004). In Finland, this percentage is twenty-one (Mattila et al. 2005). Nevertheless, the most common complaint after discharge concerns pain (Segerdahl et al. 2008). Postoperative pain delays discharge, causes discomfort and interferes with daily activities and rehabilitation. Pain is the main reason for unanticipated hospital admission (Coley et al. 2002, Mattila et al. 2009, Stomberg et al. 2013). Unplanned contacts after discharge as result of pain are regular, as shown in a Finnish study by Mattila and coworkers. Thirty-one percent of these contacts were due to pain (Mattila et al. 2005). Though the development and introduction of new analgesic drugs and techniques have been rapid, also the surgical procedures carried out have become more complex.

The procedure performed is related to pain extent. Neurosurgery (microdiscectomy), orthopaedics and abdominal surgery are reported to be among the most types of painful day surgery (Coley et al. 2002, McGrath et al. 2004). A typical orthopaedic outpatient procedure, shoulder surgery, is cited to cause the worst pain with an incidence of over

45 % for moderate to severe pain (McGrath et al. 2004) and 20 % of the patients have maximum pain scores (Wilson et al. 2004). However, a recent study has not supported these arguments but showed opposite results (Stiglitz et al. 2011). Forefoot surgery has been defined as consistent and painful for 2 to 3 days (Mattila et al. 2010) but also studies reporting generally low pain scores and with a slight need for opioid rescue analgesic have been published (Turan et al. 2008, Brattwall et al. 2010). Pain scores after knee arthroscopy are overall low and decrease rapidly over time, with the most need for analgesics occurring on the evening of surgery (Jacobson et al. 2006). According to a large prospective cohort study that evaluates pain scores on the numerical rating scale (NRS), pain scores (median) on the first postoperative day after shoulder arthroscopy were 5.0-6.0, after surgical correction procedures of toes and metatarsus and arthrodesis of toe joint 4.5-6.0, after knee arthroscopy 4.0-5.0 (Gerbershagen et al. 2013). In that study, they also noticed that patients undergoing minor procedures reported often high pain scores most probably related to insufficient pain treatment.

The strongest association, with acute postoperative pain after day surgery according to one study, was the presence of preoperative pain (Gramke et al. 2009). Other predictive factors, in this study, were the anticipated pain by a clinician and the expected pain by a patient, younger age (under 45 years versus over 60 years old) and fear of the after-effects of operation (Gramke et al. 2009). They found no consistent association between postoperative pain and sex, level of education or pain catastrophizing. This is contrary to a Finnish study that shows that female gender increases the risk for nearly all postoperative symptoms (Mattila et al. 2005). The limited effect of psychological factors on pain in the study of Gramke was explained partly by the nature of day surgery with less emotional distress.

Pain is a subjective experience and is influenced by socio-cultural, psychological and genetic factors. One significant psychological factor in the experienced severity of acute postoperative pain is catastrophizing (Khan et al. 2011). One candidate gene, with high interests, and is involved in pain perception is the catechol-*O*-methyltransferase (COMT) gene. Its polymorphisms contribute to the variability of pain perception, like sensitivity to noxious stimuli and severity of pain that vary between the subjects (Diatchenko et al. 2006). In the study investigating the effects of psychological variables and the COMT genotype on pain ratings in shoulder patients, it was found that patients, who had high pain catastrophizing scores (PCS) and a low COMT activity, reported significantly higher pain scores both pre- and postoperatively compared to those with a high PCS and a high COMT activity, a low PCS and a low COMT activity or a low PCS and a high COMT activity (George et al. 2008). They assumed that these factors might have an influence on pain perception also in other musculoskeletal pain conditions.

2.2.2. Postoperative and postdischarge nausea and vomiting

Though pain is the most frequent postdischarge symptom, there are also other symptoms and adverse effects that affect recovery, daily activities and the quality of life of outpatients. Partly, these adverse effects may be a result of pain management

with opioids when they are often dose-related but also anaesthesia and surgery itself may cause symptoms like nausea and emesis. In fact, nausea, with a high incidence, is one of the most detrimental symptoms after pain. Besides in a Finnish study, 30 % of patients requiring hospital admission from the ambulatory unit were due to PONV (Mattila et al. 2005).

After specific surgery, for example gynecological procedures, and general anaesthesia with inhalation anaesthetics the percentages of postoperative nausea and vomiting (PONV) was as high as 37 % during hospitalization and even half of the patients suffered from nausea at some point during the first three days (Parra-Sanchez et al. 2012). Patients with PONV needed more effort from nurses and stayed longer in the recovery room, which was the main reason for extra costs for patients experiencing PONV, according to a recent study from North America (Parra-Sanchez et al. 2012). Their cost analysis showed a 75 U.S. dollar cost difference when evaluating patients without nausea. This is the same amount that has been earlier defined the sum, which patients having nausea are willing to pay for antiemetics (Gan et al. 2001). Accordingly, nausea and vomiting are in second place, right after pain, on the preference list of outpatients with what they want to avoid after surgery (Jenkins et al. 2001).

Similarly, some anaesthetic methods and agents are known to be ematogenic, inter alia inhalational anaesthetics and opioids (Apfel et al. 2002, Apfel et al. 2012). However, the use of inhalational anaesthetics increases the incidence of PONV only during the first two postoperative hours but has no impact after that (Apfel et al. 2002). Other known predictors are female gender, a history of PONV or motion sickness, non-smoking status and postoperative opioid use (Apfel et al. 1999). Thus the nature of PONV is multifactorial, and now there is also evidence of a genetic susceptibility for PONV (Janicki et al. 2011). In a study analysing genotypes of 122 patients, who have suffered for PONV multiple times, a single nucleotide polymorphism (SNP) was found to be related to PONV (Janicki et al. 2011).

Also nausea and vomiting after discharge (PDNV) is common. According to one review the overall incidence of nausea after discharge was 17 % but the variation was wide. The variation had a range of zero to 55 % and there were significant heterogeneity in study methods and data collections (Wu et al. 2002). However, these numbers are in agreement with a Finnish study of more than 2000 outpatients, which showed similar overall incidence of postdischarge nausea (21 %) and vomiting (6 %) (Mattila et al. 2005). Though PDNV is most experienced by the patients who have had symptoms already at the hospital (three-fold increase in risk for PDNV) (Apfel et al. 2012), 14 to 36 % of patients with nausea have symptoms only after discharge (Parra-Sanchez et al. 2012, Wu et al. 2002). Nearly one out of ten Finnish patients had an unplanned contact to healthcare after discharge, with PDNV being in response for two percent of these contacts (Mattila et al. 2005). Predictors for PDNV are earlier PONV, nausea in the recovery room and opioid use. Surprisingly, a non-smoking status was not a predictor (Apfel et al. 2012).

2.2.3. Other postdischarge symptoms and adverse effects

With regard to pain, many other symptoms are more often experienced by younger patients (with an age under 45-50 years) and also in patients who have undergone extended surgery (a duration more than an hour) (Mattila et al. 2005, Apfel et al. 2012). Also surgical approach, as certain types of procedures like laparoscopy, predicts these symptoms in hospital, but no more after discharge (Apfel et al. 2012).

The incidences of drowsiness (ranging from 11 to 62 %) and fatigue or tiredness (ranging from 19 to 54 %) are remarkable (Wu et al. 2002, Mattila et al. 2005). Other symptoms frequently described are headache, dizziness, voiding difficulty and bowel dysfunction. These minor sequelae may not always be expressed by patients by themselves without a specific question and can often be neglected, although they may interfere with daily life and activities at home. In fact, one-fourth of the patients still reported postdischarge symptoms a week after surgery (Mattila et al. 2005). Therefore the instruments for evaluating patients' functional recovery and quality of life, instead of focusing only on single symptoms, are developed and used for assessments in postoperative recovery over the recent years (Hays et al. 2001, Wong et al. 2009, Mattila et al. 2012).

2.2.4. Unplanned admission and readmission rates

The readmission rates (hospital admission after discharge), in general, have varied from as little as 0.08 % (McGrath et al. 2004) to 1.5 % (Coley et al. 2002). The percentage needing medical advice is up to 13.4 % (McGrath et al. 2004). This is in line with a recent American multicentre study reporting an unplanned admission (admission from the ambulatory unit) rate of 1.1 % (Mathis et al. 2013). They identified 15 independent predictors of increased risk for unplanned admission: age 51-60 years, age 61-70 years, age 71-80 years, age 81-90 years, underweight BMI, obese BMI, diabetes mellitus, COPD, previous PCI/cardiac surgery, hypertension, renal failure/dialysis, history of TIA/CVA, paraplegia or quadriplegia and current steroid use. Interestingly, the male gender and a previous operation within 30 days were associated with a decreased risk (Mathis et al. 2014).

A large and recent Danish study with near 60 000 patients reported the overall rate of hospital return visits to be 1.21 % and readmissions of all other patients (including children) except those having tonsillectomy or adenoidectomy at 0.58 % (Majholm et al. 2012). The given reasons were mainly surgical in this study. However, no specific explanations were given to unplanned admissions, whose rate was 0.19 %, (Majholm et al. 2012). In Finnish studies, the unplanned admission rates of adult patients have been higher and varied from 4.9 % (Mattila et al. 2005) to 5.9 % (Mattila et al. 2009) and readmission rates from 0.3 to 0.8 %, respectively. A return to the hospital has been reported in 0.4 % of cases during the first 24 postoperative hours and 4.1 % during the first month (Mattila et al. 2009) and all unplanned contacts to health care, including telephone contacts were 9 % of cases (Mattila et al. 2005). Orthopaedic surgery accounts for most of unplanned admissions occurring at Swedish hospitals according to the feedback from seventy-nine hospitals (Segerdahl et al. 2008). A Spanish study

evaluated the data of 10 000 orthopaedic patients operated between 1993 and 2012. Their rate for admission was 0.14 % and readmission within 24 hours was 0.06 % (Martín-Ferrero et al. 2014). The study, however, included also small procedures like biopsies. Local anaesthesia was used even in 25 % of cases, and general anaesthesia only in less than 1 %. Therefore, the average intraoperative time in an operation room was only 27 minutes.

In Denmark, 0.84 % of the foot and ankle surgery patients, 0.78 % of the patients undergoing knee operations and 0.19 % of the shoulder surgery patients return back to hospital (Majholm et al. 2012).

2.2.5. Patient compliance and adherence

Earlier the word compliance was used to describe the extent to which the patient's behaviour matches to the given medical and health recommendations. However, many authors consider this term authoritarian because it makes patients look passive in a patient-doctor relationship (Osterberg et al. 2005). Besides, it was thought to reflect patient's attitude and willingness to follow the instructions. Also, the inconsistent use of "compliance" in the literature has led to replacement of the term to "adherence", which has a less negative tone and is thought to sound less non-judgemental (Haynes et al. 2009).

Medicines are seldom used as prescribed (Haynes et al. 2009). This phenomenon is old because already in 1979 there was an article that reported a typical adherence rate of 50% (Sackett et al. 1979). It is not associated with any specific somatic disease or its severity (Haynes et al. 1979b) but a low adherence had an impact on all self-conducted treatments (Haynes et al. 2008).

Though almost 30 % of patients experienced moderate or severe pain according to one study, 87 % of them regarded to managed their pain at home (McGrath et al. 2004). Despite the given instructions, many patients did not take their pain medication, not even while they had pain (Wilson et al. 2004). There are many explanations for this behaviour but most concerns are fear of addiction and possible adverse effects (Beauregard et al 1998). Also unclear, forgotten or even missing instructions resulted in the omitting of analgesics (Beauregard et al. 1998, McGrath et al. 2004). However, there are patients who neglect the given instructions and take analgesics independently on an as-required basis as was seen in a study defining the pain at home after shoulder surgery (Wilson et al. 2004).

The matter of compliance or non-compliance, adherence, or non-adherence is not limited only to medication but concerns also other instructions given to patients. Patients coming to outpatient procedures are usually prohibited to drive a car, drink alcohol or make important decisions. They also need an escort to take them home and stay overnight with them. Studies show that these rules are to some extent disregarded – about 4 % of the patients drove vehicles, 1.3 to 4 % stayed the night alone and 1.8 to 3.3 % consumed alcohol (Laffey et al. 1998, Correa et al. 2001, Cheng et al. 2002).

2.3. Pain management in day surgery

As pain is one of the main reasons responsible for unplanned hospital admissions and delays in discharge, adequate pain management is crucial for successful discharge. Pain causes not only human suffering but disturbs recovery and daily activities. Another point of view is its economical impact. Both inadequate pain management and effective anaesthetic techniques, with possible disposable equipments, cause costs that must be balanced.

2.3.1. Multimodal analgesia

Kehlet introduced the term “multimodal analgesia” in year 1993 (Kehlet et al. 1993), and since then, it has become the standard care in modern day surgery. Nowadays, multimodal analgesia is a combination of different analgesics and/or analgesic techniques used in order to improve pain management by utilising their additive or even synergistic effects. The purpose is also to minimise the adverse effects of a single drug or method. Multimodal analgesia is considered as the key to accelerating a return back to daily life and normal activities, as low pain scores are not a goal itself but rather lead to mobilisation and rehabilitation (White et al. 2007).

Nonsteroidal anti-inflammatory steroids and paracetamol are primary pain management treatments to outpatients. They are both proved to have effect on postoperative pain when used alone (Sinatra et al. 2005, Göröcs et al. 2009, White et al. 2011), but in combination the effect is superior (Ong et al. 2010). In this review article 17 out of 20 studies (85 %) showed that a combination of paracetamol and NSAID improved pain care compared with paracetamol alone, and in orthopaedics the advantage of this combination was seen in 80 % of the studies. Compared with NSAIDs alone, in turn, the combination was more effective in nine studies out of 14 (64 %), and in orthopaedics this difference was noticed in half of the studies. In subgroup analysis of both comparisons; i.e., paracetamol alone vs. combination with NSAID and NSAID alone vs. combination with paracetamol, the combination with ketoprofen turned out to have 100 % success in both comparisons, ibuprofen had 100 % and 67 % success, respectively.

A Finnish study shows that 73 % of their outpatients were prescribed NSAIDs and only 4 % of paracetamol (Mattila et al. 2005). Paracetamol with codeine was prescribed for 13 % of the patients. However, data of medicine used at home was missing in 19 % of responses. Multimodal analgesia is common in Sweden, where 71 out of 76 units used drug combinations (Segerdahl et al. 2008). The combination of paracetamol and NSAIDs was used by 19 units and additional weak opioid was used by 32 units. Swedish outpatients received paracetamol as take-home medication from 58 % of units. This was followed by a prescription in 36 % of the cases (Segerdahl et al. 2008).

Local anaesthetics, administered by many different routes, have long been used for intra- and postoperative analgesia. In addition to the regional anaesthesia, that can be divided into a central neuraxial block, a peripheral nerve block and a field block

(Latifzai et al. 2008), local anaesthetics have been used intravenously. The term intravenous regional anaesthesia is used for a Bier block but intravenous local anaesthetic, mainly lidocaine, has also been administered for postoperative pain care (Vigneault et al. 2011). As the number of the patients having medicines that affect blood coagulation has increased and continuous central neuraxial blocks are not suitable for day surgery, peripheral blocks have gained a large popularity recently. Also new devices, like ultrasound, have changed contemporary attitudes towards these blocks and lessened some complications, like vascular punctures (Danelli et al. 2012). Efficient pain management can be prolonged by using continuous local anaesthetic infusions *via* perineural or wound catheters, which are especially adopted to orthopaedics.

Depending on purpose, there are many local anaesthetics to select. In day surgery, the fast recovery of the patients is important, and therefore short-acting local anaesthetics, like articaine and chloroprocaine (Förster et al. 2013), or small doses of long-acting local anaesthetics, like bupivacaine, levobupivacaine and ropivacaine (Valanne et al. 2001, Cappelleri et al. 2005), are often used for spinal anaesthesia. For pain management, long-lasting agents are more suitable. In a study evaluating peripheral nerve blocks for pain management after foot and ankle surgery, no superiority was noted between bupivacaine, levobupivacaine and ropivacaine (Wang et al. 2014).

The perioperative use of glucocorticoid steroids has aimed traditionally at preventing and reducing nausea and vomiting. They may also have benefits in reducing postoperative pain and improving recovery, when used as part of multimodal analgesia. However, the opinions of dosing; e.g., of dexamethasone, are conflicting, as there are studies showing this benefit already after a single small-dose dexamethasone (Bisgaard et al. 2003, Murphy et al. 2011), whereas some studies show these effects only after intermediate (0.11-0.20 mg/kg) or high-dose (≥ 0.21 mg/kg) administration (Jokela et al. 2009, De Oliveira et al. 2011). Only doses more than 0.1 mg/kg, which has been defined the upper limit of low-dose, was effective in reducing opioid consumption or pain scores in the postoperative phase in one meta-analysis (De Oliveira et al. 2011). However, a recent review showed that single dose dexamethasone (1.25-20 mg) had a significant opioid sparing effect, but no clinically significant association between doses of dexamethasone and opioid consumption were found (Waldron et al. 2013). Also, repeated dosing has been used as a part of multimodal analgesia (Mattila et al. 2010).

Though much of the use of multimodal analgesia is based on avoiding the adverse effects of opioids, they still have a place in pain management in moderate and severe pain. Weak opioids, like codeine and tramadol, may be combined with paracetamol and NSAIDs, which are the most common combination for pain management after day surgery, at least in Sweden (Segerdahl et al. 2008). Weak opioids are also frequently prescribed for home use, and strong opioids, occasionally. However, almost two-thirds of the Swedish units provided strong opioids as take-home medication (Segerdahl et al. 2008). According to a Finnish study, weak opioids were prescribed for 18 % of the patients (Mattila et al. 2005). There are some problems related to weak opioids. Both codeine and tramadol are pro-drugs and their analgesic properties depend on conversion to active drugs. Codeine is converted to its active metabolite morphine and

tramadol to O-desmethyl-tramadol by cytochrome P 450 2D6. Because of the large inter-individual variation in codeine metabolism, 7-10 % of Caucasians are poor metabolisers and do not benefit from codeine use (Agúndez et al. 1995, Sachse et al. 1997), and on the other hand, one percent of Swedish people (Dahl et al. 1995), from one to eight per cent of Finnish population (Saarikoski et al. 1999), seven per cent of Spanish (Agúndez et al. 1995) and 29 % of Ethiopians (Aklillu et al. 1996) are ultrarapid metabolisers, whom are at risk for opioid overdose. Also, tramadol uses the same enzyme CYP2D6 for its metabolism. For the same reasons, there are patients, which have no analgesia while using tramadol (Stamer et al. 2003).

According to a recent European survey defining variations and routines of day surgery in eight countries the use of analgesics already in preoperative phase is common (Stomberg et al. 2013). Ninety-four percent of the units used paracetamol, 80 % NSAIDS, and 28 % opioids. In Finland, six of the ten studied hospitals used peroral analgesics preoperatively but not opioids. Fifty-nine percent of seventy units in the studied eight countries instructed the use of strong opioids at home when considered necessary.

2.3.2. Intrathecal clonidine

Clonidine, an α_2 -agonist, is long known to have analgesic properties that can benefit in improving the quality of anaesthesia and analgesia. When administered intrathecally or epidurally the main action sites of clonidine are the pre- and post-synaptic α_2 -receptors in the dorsal horn. It blocks the conduction of C and A δ fibres. The onset of analgesia is rapid and dose-dependent. Three hundred or 450 μg of clonidine intrathecally can produce almost immediate analgesia (Filos et al. 1994) but even a dose as small as 25 μg can cause significant analgesia to heat pain (Ginosar et al. 2013). Clonidine, when used alone, does not cause motor block or weakness.

Clonidine can be combined to opioids, local anaesthetics and to a mixture of both of them. A clonidine dose of 1 $\mu\text{g}/\text{kg}$ combined with intrathecal morphine reduced the need of intraoperative opioid as well as prolonged the time until the first request for a rescue analgesic when compared with morphine alone (Andrieu et al. 2009). A combination of morphine, clonidine (25 or 75 μg) and local anaesthetic has been used for surgery of total knee arthroplasty, the benefit of clonidine was clearly identified, seen as lower VAS scores and reduced morphine consumption, compared with a bupivacaine-morphine combination (Sites et al. 2003). By contrast, patients undergoing hip replacement received intrathecal clonidine (75 μg) and morphine (0.5 mg) for postoperative analgesia with no significant differences compared with morphine alone, except hypotension, that appeared statistically significantly more often in the former group (Grace et al. 1995).

As an adjunct to local anaesthetic in central neuraxial blocks, clonidine has been shown to prolong motor and sensory block either measured by a return of sensation or by an additional analgesic request (Racle et al. 1987, Niemi 1994, van Tuijl et al. 2008). One explanation that has been offered is that the cellular modification by clonidine in the ventral horn of a spinal cord and the facilitation of the action of local anaesthetics (De Kock et al. 2001).

A study establishing intrathecal clonidine doses that would prolong spinal anaesthesia without significant adverse effects, like hypotension, bradycardia and sedation, in orthopaedic patients found prolongation to be dose-dependent (Strebel et al. 2004). They ended up recommending a dose of 150 µg, which was the maximum dose, administered in this study. Controversially, a meta-analysis ended up in a conclusion that only sensory block was linearly dose-related, and moreover, they were not able to demonstrate a dose-related risk for hypotension or any impact of clonidine on bradycardia (Elia et al. 2008).

The effect of clonidine use is favourable for reducing pain. However, day surgery aims to optimize anaesthesia without delayed discharge. There are several studies defining the most favourable doses of both clonidine and local anaesthetic for outpatient procedures. Van Tuijl et al compared 5 mg hyperbaric bupivacaine (5 mg/ml) alone with combination of 15 and 30 µg of clonidine diluted with saline to a volume of 3.0 ml (van Tuijl et al. 2008). Both concentrations of clonidine prolonged the motor block. The time to complete recovery from motor block lasted 25 and 34 minutes (patient weight adjusted), respectively, longer than the recovery of 70 minutes in the bupivacaine group. The difference between clonidine 15 and clonidine 30 µg was not statistically significant. Also, the time to voiding was prolonged with 18 and 44 min, respectively, but significantly only in bupivacaine-clonidine 30 µg group. The need of additional analgesics or anaesthesia intraoperatively was reduced in those receiving clonidine but there was also a tendency towards increased use of vasopressor. They concluded that the addition of clonidine to 5 mg of hyperbaric bupivacaine improves spinal anaesthesia for outpatient knee arthroscopy but preferred the dose of 15 µg over 30 µg. Also, De Kock et al. studied patients undergoing knee arthroscopy. They compared plain ropivacaine with three different doses (15, 45 and 75 µg) of clonidine combined with 8 mg of isobaric ropivacaine (group 2, 3 and 4) in a volume of 4 ml (De Kock et al. 2001). They found that a clonidine dose of 15 µg was most suitable as it improved the quality of anaesthesia. Though this dose prolonged motor blockade, time to walking was not significantly longer compared to plain ropivacaine. A delay in walking was 25 minutes (mean time to walking 158 minutes in group 2) and in time to voiding 19 min (mean time to voiding 189 minutes in group 2). Groups with clonidine doses at 45 and 75 µg were associated to lower arterial blood pressure, and sedation was detectable in group with a clonidine dose of 75 µg. These adverse effects were apparent in an older study using clonidine dose as high as 3 µg/kg and bupivacaine dose of 15 mg for knee arthroscopy (Niemi 1994).

Dobrydnjov et al ended up recommending for the same dose of additional clonidine, as in above mentioned studies; i.e., 15 µg, combined with 6 mg of hyperbaric bupivacaine for inguinal herniorrhaphy (Dobrydnjov et al. 2003). Bupivacaine 6 mg, bupivacaine 6 mg plus clonidine 15 µg and bupivacaine 6 mg plus clonidine 30 µg were all diluted with saline to a total volume of 3 ml. Additionally, they defined unilaterality of the block and found that number of patients having a unilateral block was lower in clonidine groups. There were no differences in recovery parameters (standing, walking, time to first urination) between those receiving plain bupivacaine and those receiving additional clonidine of 15 µg. However, pain scores were significantly lower during the first 3.5 hours in clonidine groups compared to bupivacaine groups, as well as the

mean arterial pressure. Despite of improved anaesthesia, the use of clonidine is not a routine in day surgery.

2.3.3. Subacromial bupivacaine

The idea of subacromial bupivacaine, or other local anaesthetic, is to administer it directly into the surgical site to provide effective analgesia postoperatively. Shoulder surgery, including shoulder arthroscopy, has reported to cause severe postoperative pain (Barber et al. 2002, Wilson et al. 2004, Fontana et al. 2009), which demands effective pain management. Besides, shoulder arthroscopy is typically an outpatient procedure; consequently pain management must be simple to use and without adverse effects. Many pain management modalities such as NSAIDs and opioids perorally or intravenously, intra-articular or subacromial local anaesthetics and/or morphine (Barber et al. 2002, Park et al. 2002) and different nerve blocks (Fontana et al. 2009) have been in use, many as part of multimodal analgesia. Interscalene plexus block is known to have superior efficacy on postoperative pain after shoulder surgery (Al-Kaisy et al. 1998, Hughes et al. 2013), especially when continuous analgesia *via* a catheter is used (Borgeat et al. 2002, Ilfeld et al. 2003). However, there are conflicting reports and studies concerning success rates in the past. Because of unsuccessful blocks, catheter insertion and dysfunctional pumps, a failure rate of continuous interscalene block has been reported to be even 25 % in some older studies (Tuominen et al. 1989, Ilfeld et al. 2003), though there are also studies describing success rates of 96 to 97 % (Borgeat et al. 2003, Fredrickson et al. 2008). Therefore, less demanding and invasive techniques were developed.

During the early 2000s, subacromial local anaesthetic gained popularity attributable to its simplicity, riskless and time-sparing (compared to interscalene) but still efficient qualities (Savoie et al. 2000, Barber et al. 2002). The block is carried out by a surgeon whom injects local anaesthetic or inserts a catheter for continuous infusion into subacromial space verified by arthroscopic vision at the end of surgery. Early studies have showed the effectiveness of continuous subacromial block. Barber et al. evaluated the method by randomising patients undergoing shoulder arthroscopy to have either 0.5 % bupivacaine or saline at 2.1 ml/h subacromially (Barber et al. 2002). The routine was also to administer 10 mg morphine intra-articularly or intrabursally. The mean pain scores of those having bupivacaine infusion were significantly lower than those having saline. The highest pain scores on the visual analogue scale (VAS) were 5.6 and 6.8, respectively, on the first postoperative day. The difference in the use of supplemental analgesics was not significant though there was a tendency for lower use in bupivacaine infusion group. Earlier Savoie et al. found a decrease both in pain scores and analgesic consumption already with an infusion rate of 2 ml/h of 0.25 % bupivacaine (Savoie et al. 2000). Coghlan et al. used subacromial ropivacaine (7.5 mg/ml, 5 ml/h) for postoperative pain after arthroscopic subacromial decompression and rotator cuff repair (Coghlan et al. 2009). Also, they discovered a statistically significant improvement in average pain in the first twelve hours compared with placebo. However, this improvement was considered clinically unimportant. The differences in the mean pain scores on the verbal analogue scale were 0.5 and 0.7,

respectively. Moreover, no significant difference was found in opioid or oral analgesia use or average pain in the next twelve hours. The writers considered that there were no observable benefits that would advocate costs caused by a disposable pump, a catheter and local anaesthetic. Furthermore, the study was hampered by technical issues, as the flow rates of the infusion varied considerably being more rapid than 5 ml/h in 94 % of patients. Inaccurate flow rates, usually faster infusion than programmed, have been reported (Ackermann et al. 2007), as well as decreased flow rates or no deflation at all (Remerand et al. 2008).

2.3.3.1. Toxicity of bupivacaine

Bupivacaine, a widely used, long-lasting local anaesthetic, is a potentially toxic compound and it may accumulate during continuous infusion. Official recommendations for a maximum single dose (150 mg for bupivacaine) (Orion, Finland) and cumulative daily doses of bupivacaine (400 mg/24 h) (Orion, Finland) or other local anaesthetics, are not evidence based and do not take into consideration, e.g., injection site (Rosenberg et al 2004). Systemic toxicity may occur after unintentional intravascular or intrathecal injection of bupivacaine but also peripheral tissue and nerve injections or infusions with excessive dose may lead to neurological and cardiovascular complications.

There has been a huge reduction in the incidence of toxicity of local anaesthetics due to notification of safety issues since 1980s. A study analyzing brachial blocks performed between years 1985 and 1992 reported the frequency of seizures as a sign of systemic toxic reactions to be 2.0 per 1000 brachial plexus block (Brown et al. 1995). However, if brachial blocks, where bupivacaine has been used, are regarded, the rate increases up to 3.5 per 1000 blocks. In a later study during the 1990s, the incidence of seizures was 0.75 per 1000 undefined peripheral nerve blocks (Auroy et al. 1997). It is quite similar with 0.98 per 1000, the incidence of overall systemic toxicity after plexus block, reported by a review study in the 2000s but higher than the incidence of seizures and unconsciousness, which was only 0.37 per 1000 blocks (Barrington et al. 2009). Bupivacaine was used only in 3 % of the blocks in that study. Even when block is performed with ultrasound-guidance, unintentional intravascular injections are possible. The incidence of arterial puncture was 1.2 per 1000 ultrasound-guided nerve blocks, though there was only one case of seizures in the study of over 12 000 patients the incidence being 0.08 per 1000 (Sites et al. 2012). Symptoms of toxicity may also occur with a 20-30 minute delay after perineural administration, as injected bupivacaine is absorbed to the systemic circulation (Mulroy 2002).

After intravenous bupivacaine infusion in volunteers most of the symptoms from central nervous system (CNS) have occurred at total plasma concentrations between 1-2 µg/ml in venous blood (Scott et al. 1989). Similarly in another study, where *iv*-infusion was used, the maximum tolerated total plasma concentration was 2.1 (mean, SD 1.2, min-max 0.8-4.5) and unbound 0.11 (SD 0.10, min-max 0.01-0.38) in venous sample (Knudsen et al. 1997). In the arterial sample, the concentrations were twice of those: 4.0 (1.4) and 0.30 (0.11), respectively. The QRS complex in the ECG was widened in nine out of 12 volunteers but not the PQ or QTc interval. The prolongation

of PQ interval was seen after a single dose of 5 mg/ml in 40 ml bupivacaine for the interscalenic plexus block (Borgeat et al. 2004). However, no other changes in ECG were noticed in this study. The highest mean total and unbound plasma concentrations of bupivacaine were 1.38 and 0.084 $\mu\text{g/ml}$, and the highest individual unbound plasma concentration was 0.12 mg/ml. In another study, where an initial bolus of 20-28 ml of 7.5 mg/ml bupivacaine for interscalenic block was used and constant infusion of 2.5 mg/ml bupivacaine at a dose of 0.25 mg/kg was commenced immediately, the highest concentrations were measured at 30 and 60 minutes (Rosenberg et al. 1991). The maximum mean total bupivacaine concentration was 1.63 (SD 0.55) $\mu\text{g/ml}$. The highest individual total concentration was 3.25 $\mu\text{g/ml}$ without any toxic symptoms (Rosenberg et al. 1991). In a similar setting but with a smaller initial bolus (5.0 mg/ml bupivacaine at a dose of 1.25 mg/kg) lower concentrations were measured: the highest mean and individual total bupivacaine concentration were 0.76 $\mu\text{g/ml}$ (SD 0.10) and 2.3 $\mu\text{g/ml}$, respectively, at 24 hours (Tuominen et al. 1987). In that study, two patients reported metallic taste during bupivacaine infusion but the symptoms were not considered toxicity-related and the infusion was continued. Though there are studies determine bupivacaine plasma concentrations after interscalene and epidural block and continuous perineural infusions, we have found no studies evaluating bupivacaine concentrations after continuous subacromial infusion.

Bupivacaine is highly bound to plasma proteins, mainly to α_1 -acid glycoprotein (AAG), and it is the unbound fraction that is active (Denson 1984, Tucker 1986). Veering et al. evaluated the concentrations of plasma bupivacaine and AAG during epidural bupivacaine infusion (Veering et al. 2002). They demonstrated that total plasma concentrations of bupivacaine increase progressively but the concentrations of unbound bupivacaine reach a plateau between 12 to 24 hours. This was explained by an increase of AAG concentrations. The same finding was done earlier by Rosenberg et al. (Rosenberg et al. 1991). Surgery is long known to increase the concentration of AAG within 24 hours (Aronsen et al. 1972, Wulf et al. 1989).

The main metabolites of bupivacaine are desbutylbupivacaine (DBB) and 4-hydroxybupivacaine (4-OHB) (Boyes et al. 1975), and also they are shown to accumulate during bupivacaine infusion (Rosenberg et al. 1991, Pere et al. 1991). DBB is less toxic than bupivacaine with a lethal dose, 50 % (LD_{50}) of intravenous DBB in mice was shown to be 63 mg/kg, which is eight times of that found for bupivacaine (Hansson et al. 1965). When DBB was given intraperitoneally, the LD_{50} was 140 mg/kg, three-fold that of bupivacaine (Bruguerolle et al. 1994). In the same study CNS toxicity was induced by doses twice of those of bupivacaine. To our knowledge, there are no studies addressing the toxicity of 4-OHB.

Toxicity of bupivacaine is not only systemic but may also be local. When evaluating the neurotoxicity of eight local anaesthetics (articaine, procaine, licocaine, mepivacaine, prilocaine, ropivacaine, bupivacaine and tetracaine) in neuroblastoma cells, they all proved to be neurotoxic and induced cell apoptosis (Werdehausen et al. 2009). The neurotoxicity was dependent on the concentration and the lipophilic properties of the local anaesthetic. Only tetracaine was more toxic than bupivacaine. In another study, neurotoxicity of bupivacaine and ropivacaine was found in cell culture

but not in the histopathological evaluations of the sciatic nerves of rats (Cereda et al. 2012). Also myotoxicity of both local anaesthetics were confirmed after single cove in cell cultures. Though histopathologically some muscle fibre damage was characterized, no sign of myonecrosis or muscle damage was found. After six hours bupivacaine infusion into femoral nerve sheaths of minipigs, severely damaged muscle fibres were seen (Zink et al. 2003).

Chondrotoxicity of bupivacaine has caused probably the most concerns in clinical practice, as local anaesthetics has been used intraarticularly for pain relief and in treatment of osteoarthritis. In addition to *in vivo* and animal studies, there are several reports of postarthroscopic glenohumeral chondrolysis of the shoulder after intraarticular bupivacaine infusion (Hansen et al. 2007, Bailie et al. 2009, Anderson et al. 2010). Therefore the use of subacromial and intra-articular local anaesthetic infusions has been questioned. Fredrickson et al. concluded in their review article that because the method is only marginally better than placebo and is associated with devastating glenohumeral chondrolysis, it cannot be recommended (Fredrickson et al. 2010). The recommendation concerned both subacromial and intra-articular infiltration analgesia despite the fact that there are no evidences of chondrolysis after subacromial local anaesthetic infusion but intra-articular infusion (Busfield et al. 2009, Rapley et al. 2009).

2.3.4. Transdermal fentanyl

Fentanyl is a high-potency opioid - 75 to 100 times more potent than morphine - that was synthesized for an alternative to morphine in 1959. It was first introduced for intravenous use but due to its low molecular weight and high lipophilicity it became effective also for a transdermal system. Transdermal fentanyl was the first transdermal analgesic and it was approved by U.S. Food and Drug Administration (FDA, Approval History) in 1990 for a supplemental analgesic in postoperative and cancer pain (FDA). During the next five years transdermal fentanyl was used eagerly in postoperative pain management after abdominal, gynecological, orthopaedic and other procedures. The first patches delivered 25, 50, 75 and 100 µg/h fentanyl, later on a smaller patch delivering fentanyl 12 µg/h was brought to market. Initially, these were reservoir patches but because of the incidents of misuse, a novel matrix system, where fentanyl is dissolved in matrix, was developed. Already in 1991, recommendations against postoperative use were inserted in packages of fentanyl patches and in 1994 acute postoperative pain was stated as a contraindication of transdermal fentanyl. Since then, studies evaluating the use of transdermal fentanyl in postoperative pain management have been infrequent, and no studies related to day surgery have been published. Currently, FDA and European Medicines Agency have approved transdermal fentanyl only for chronic pain.

Many studies have proved the efficacy of transdermal fentanyl but have also shown typical adverse effects related to its use. Caplan et al. evaluated the use of fentanyl patches delivering fentanyl at a rate of 75 µg/h and worn for 24 hours in 42 patients undergoing shoulder surgery (Caplan et al. 1989). Transdermal fentanyl reduced the consumption of morphine significantly compared to those receiving placebo but also

increased vomiting. Respiratory rate was lower in those receiving fentanyl (mean value 14/min) compared to those receiving placebo (mean value 16/min). They concluded transdermal fentanyl to be an effective and safe method for postoperative pain after shoulder surgery in healthy adults. The patch of the same size but worn for 72 hours was used in the study of Van Bastalaere et al. with 40 orthopaedic patients (Van Bastelaere et al. 1995). Also they showed the effectiveness of transdermal fentanyl, as only 55 % patients in the fentanyl group required supplemental morphine compared to 95 % in the placebo group. However, they ended up to withdraw one patient because of respiratory depression and were therefore concerned about safety aspects. Sevarino et al were able to find no significant differences in VAS, adverse effects or total opioid consumption calculated in morphine equivalents in their study comparing 50 and 75 µg/h patches with placebo after major orthopaedic surgery having morphine PCA (Sevarino et al. 1997). Because of the lack of benefits and possible risk factors, they recommended not using two concurrent systems delivering continuous opioid.

To diminish the risks, Reinhart et al. combined the patch delivering fentanyl 75 µg/h with NSAID, ketorolac (Reinhart et al. 1997). Pruritus was the only adverse effect that significantly differed between the groups (more in fentanyl group). Still one patient having a fentanyl patch was discontinued due to bradypnoea. As there was no access for supplemental opioids after leaving the recovery room, there were significantly more dropouts due to inadequate analgesia in the placebo group than in the fentanyl group, more doses of administered ketorolac and also higher pain scores. Every fourth patient, on average, in the fentanyl group, managed without analgesic supplementation. This is the same rate as in the study using transdermal fentanyl (75 µg/h) after knee arthrotomy (Latasch et al. 1989) but less than that of 55 % in another study consisting of orthopaedic patients (Van Bastelaere et al. 1995).

There is a delay of onset when using a fentanyl patch. Fentanyl needs first to diffuse into the skin and thereafter reach cutaneous and then general circulation. This delay, defined either as an appearance of detectable plasma concentration or detectable analgesia, takes several hours. When a 100 µg/h patch was used serum fentanyl concentrations rose incrementally during the first 14 hours after a patch placement and stayed relatively constant thereafter up to 24 hours when a patch was removed (Varvel et al. 1989). Minimum effective concentrations (MEC) for abdominal surgery, 0.63 ng/ml, were obtained in 12.7 hours (mean) with patches of 50-125 µg/h (Gourlay et al. 1989). Using only a patch of 50 µg/h, the delay for analgesia has been longer, 18.9 hours (mean) (Lehmann et al. 1992). This delay time usually leads to the use of other supplemental analgesic methods in immediate postoperative pain. One solution is to apply a fentanyl patch several hours before the surgery. Minville et al. placed a 50 µg/h fentanyl patch 10 hours before hip arthroplasty in order to reach a plateau at the end of surgery (Minville et al. 2008). There was a significant difference both in morphine consumption and pain scores already on arrival at the PACU in behalf of fentanyl group. They found no significant differences in adverse effects or bradypnoea. A limitation of their study was the lack of blinding, unlike in the double-blinded study of Abrisham et al. (Abrisham et al. 2012), they placed a 25 µg/h fentanyl patch 12 hours before anaesthesia in a study determining the effects of transdermal fentanyl for postoperative pain after total knee arthroplasty. Both VAS scores and morphine

consumption were less in the fentanyl group, but adverse effects were similar between the groups.

Transdermal fentanyl has earlier been shown to produce plasma concentrations comparable to those during *iv*-infusion of fentanyl (Duthie et al. 1988). As the drug absorbs slowly at a constant rate, it produces relatively constant serum concentrations without rapid peaks and troughs, which are related to intravenous, intramuscular and oral dosing of analgesics (Varvel et al. 1989). Conflicting studies has been published subsequently reporting varying serum concentrations in single patients with a fentanyl patch (Kokubun et al. 2007, Cole et al. 2010). Intrasubject variability in fentanyl metabolism and excretion has shown to be considerably greater than previously perceived and this variation may be partly in response of the unpredictable adverse effects (Cole et al. 2010). Individual variation is widely known (Varvel et al. 1989, Cole et al. 2010) and is most probably due to metabolism (Cole et al. 2010). The primary enzyme metabolizing fentanyl is CYP3A4 but also by CYP3A5 (Jin et al. 2005). Because of the polymorphisms of these enzymes, the variation in total fentanyl load may be 30-fold between the patients using patches delivering fentanyl 12.5 to 100 µg/h (Cole et al. 2010). As for fentanyl toxicity the variation in metabolism may be one explanation. The application site of the patch, sex or weight, with the exception of the reduced absorption of fentanyl in cachectic cancer patients (Heiskanen et al. 2009) do not seem to affect fentanyl delivery. Also heating systems such as warming blankets, sauna or fever may raise the absorption of transdermal fentanyl (Newshan 1998, Frölich et al. 2001, Janssen-Cilag, Finland).

Once a patch has been removed, absorption of fentanyl still continues from the skin into the circulation. Serum concentrations of fentanyl decrease gradually to half during approximately 17 hours (Varvel et al. 1989). The extension of analgesia offers time for possible conversion of analgesic method. The downside is that also possible adverse effects continue and prompt completion of the effect of fentanyl may require administration of opioid antagonist multiple times.

Nevertheless, transdermal fentanyl provides an effective and continuous analgesia, a convenient and simple alternative for pain management, especially for those unable or unwilling to use peroral analgesics. Continuous analgesia can also offer better quality of sleep (Van Bastelaere et al. 1995) and lead to less painful awakening in morning as well as less painful morning activities (Sevarino et al. 1997) compared to other pain modalities. Compared with PCA it costs less and needs no *iv*-access. If opioid-PCA is used, there is no significant advantage in routine use of transdermal fentanyl (Sevarino et al. 1997).

3. AIMS OF THE STUDY

The objective of this thesis, consisting of five studies, was to evaluate different pain modalities and find good, safe and economic alternatives for analgesia in day surgery. Study 1 scrutinized the unilaterality of spinal block. In Studies 2, 3 and 4 all the patients underwent shoulder arthroscopy. However, Study 2 focused on safety whereas Studies 3 and 4 focused on pain. Similarly, Study 5 concentrated on postoperative pain but this was in contrast to Studies 3 and 4 where the patients underwent forefoot surgery.

The specific aims of these five studies were:

1. To assess the effect of clonidine on unilaterality of spinal block in knee arthroscopy (Study I)
2. To evaluate the safety (Study II) and efficacy (Study III) of postoperative subacromial bupivacaine infusion after shoulder arthroscopy in an outpatient setting
3. To determine the effectiveness of subacromial bupivacaine infusion compared with transdermal fentanyl in postoperative pain management after shoulder arthroscopy (Study IV)
4. To determine the effectiveness of transdermal fentanyl in the treatment of postoperative pain after hallux valgus or hallux rigidus surgery (Study V)

4. MATERIALS AND METHODS

4.1. Ethical aspects and patients

All the study protocols were accepted by the Ethics Committee of the Hospital District of Southwest Finland and also the National Agency for Medicine was notified of the study protocols. Studies III, IV and V were registered to EudraCT and III and V also to ClinicalTrials.gov database. Written informed consent was obtained from all patients prior to their recruitment in the studies. All together 276 patients were included in the analysis.

Table 2. Patients participating in Studies I-V. Data are presented as absolute numbers or mean (SD) [min-max]. Duration of surgery is reported as median [min-max]. *p-value<0.05 represents a statistically significant difference.

Study	Number of patients	Age (years)	BMI (kg/m ²)	Sex (M/F)	Duration of surgery (min)
I	30	48 (14)	26 (3) [21-35]	12/18	26 [12-61]
	30	47 (12)	27 (3) [22-31]	14/16	23 [9-61]
II	8	51 (13)	28 (3) [24-35]	3/5	48 [27-115]
	8	55 (12)	27 (3) [24-33]	4/4	83 [30-118]
III	39	53 (9)	26 (4) [19-35]	24/15	56 [27-167]
	43	55 (6)	27 (3) [22-33]	34/9	76 [27-164]*
IV	30	52 (9)	27 (4) [21-35]	11/19	63 [30-146]
	30	54 (9)	26 (3) [20-32]	14/16	60 [30-149]
V	29	56 (7)	27 (4) [21-35]	5/24	64 [25-127]
	29	53 (11)	26 (4) [20-33]	6/23	53 [27-124]

Inclusion criteria:

- Adults aged 18-75 were accepted
- ASA (American Society of Anesthesiology) physical status classification I-III
- Scheduled elective unilateral knee or shoulder arthroscopy or hallux valgus or rigidus surgery according to study protocol
- Written informed consent from the patient

Exclusion criteria:

- History of intolerance or allergy to the drugs used in the study or related compounds and additives
- Psychological or other emotional problems, which are likely to invalidate the informed consent
- History of alcohol or drug abuse
- BMI (body mass index) over 35 kg/m² except in Study II

Specific contraindications were:

- Heart rate < 50/min, PR interval > 0.2 s, QTc > 440 ms, contraindication for spinal anaesthesia in Study I
- Liver diseases or kidney impairment in Study II and III
- Obstructive sleep apnoea in Study IV and V

Patients were judged to have liver disease or renal impairment if they had a clinical diagnosis of this type or clinically significantly increased liver enzymes or serum/plasma creatinine. However, patients with diabetes mellitus were eligible unless they had a significant renal involvement diagnosed earlier. Only in Study II serum creatinine and alanine amino-transferase were taken pre-operatively.

4.2. Study designs

Studies were performed between 2005 and 2010 at the Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine at the Surgical Hospital of Turku University Hospital. All studies were randomised, double-blinded placebo or active-controlled studies.

Peroral paracetamol 1 g was used as premedication an hour before surgery except in Studies I and II, where no premedication was in use. In Study II, paracetamol was administered intravenously in the intraoperative phase, as well as in Studies III and IV together with ketoprofen. In addition to specific study drugs, patients in the four studies received ibuprofen and/or paracetamol regularly during the postoperative phase, and oxycodone if needed, during hospital stay. In Study II, a PCA-device filled with morphine was used instead of oxycodone. For pain management at home patients received a prescription of ibuprofen and paracetamol, in Study III paracetamol combined with codeine, in addition to four oxycodone 10 mg tablets given from hospital in Studies III, IV and V.

The anaesthesia method of Studies I and V was spinal anaesthesia, and total intravenous anaesthesia with remifentanyl and propofol was used in Studies III, IV and V.

Patients in all the studies were monitored continuously from the beginning of anaesthesia until leaving the recovery room. Standardised monitoring consisted of noninvasive arterial blood pressure measuring at 5-min intervals, electrocardiogram and peripheral arterial oxygen saturation. In addition to these, end tidal carbon dioxide-concentration and bispectral index were monitored continuously in patients having general anaesthesia.

4.2.1. Study I

The study consisted of 60 patients undergoing knee arthroscopy under spinal anaesthesia. If needed, midazolam or fentanyl for pre- and intraoperative sedation was administered. Patients were randomised to receive either hyperbaric bupivacaine (5

mg/ml) 6 mg (1.2 ml) or hyperbaric bupivacaine 5 mg (5 mg/ml) (1.0 ml) with clonidine 15 µg (0.1 ml) and sterile-distilled water 0.1 ml. Spinal anaesthesia was performed at the LIII-LIV interspace in the lateral position, which was maintained 10 minutes after local anaesthetic injection. Patients were discharged when they were able to walk, void and if also their vital signs were stable, they had only minimal or no pain at all, they had no postoperative nausea or vomiting and there was no bleeding.

Both motor and sensory block were tested bilaterally 10, 20 and 30 minutes after spinal injection, immediately after operation, 2 hours after spinal injection and every 15 minutes thereafter until motor block was totally resolved. A modified Bromage scale was used to evaluate motor block, accordingly hip flexion, knee extension, ankle dorsiflexion, great toe dorsiflexion and ankle plantar flexion were assessed. The scale was from zero (no block) to one (a complete or partial block). Sensory block was tested using a pinprick test. Pain at rest and on movement, nausea and sedation were monitored using VAS (0-10).

After surgery, the patients and the surgeon were asked their opinion of anaesthesia - whether it was good, satisfactory or poor. Patients answered also to the question about quality of anaesthesia. The options of a four-point scale were: perfect analgesia: no sensation at all from the surgical site; adequate analgesia: sensation of motion only; inadequate analgesia: discomfort, but no additional analgesia needed; major discomfort: additional analgesics necessary.

4.2.2. Study II

Sixteen patients scheduled for shoulder arthroscopy received either bupivacaine 2.5 or 5.0 mg/ml subacromially according to randomisation. At the end of surgery, a surgeon inserted a multiorifice epidural catheter subacromially and injected a bolus of 100 mg of bupivacaine (5.0 mg/ml) with adrenaline. A continuous infusion rate was 2 ml/h *via* an infusion pump (Infusor, Baxter Healthcare Corporation). For rescue analgesia, a PCA pump with morphine, was used during the first 24 hours, thereafter patients received peroral analgesics.

The total plasma concentrations of bupivacaine and its metabolites 4-hydroxybupivacaine (4-OHB) and desbutylbupivacaine (DBB), were determined before surgery, 30 minutes, 1, 2, 6, 24 and 48 hours after the bolus of bupivacaine. At the time of 24 and 48 hours, also α_1 -acid-glycoprotein (AAG) was measured. The concentrations of bupivacaine, 4-OHB and DBB were determined using a modification of a previously described method (Ledger 2003) and a liquid chromatography-tandem mass spectrometer system (SCIEX Q Trap LC/MS/MS system). The limit of quantification was 0.0005mg/ml for bupivacaine, 4-OHB and DBB. The inter-day coefficient of variation was $\leq 7.7\%$ for bupivacaine and both its metabolites at relevant concentrations. Pain scores using NRS at rest and in movement were evaluated at the same intervals as bupivacaine concentrations, possible adverse effects and morphine consumption was registered.

Patients were discharged after 24 hours and they returned at 48 hours for blood samples and to have the infusion device to remove. They were asked about possible

adverse effects related to local anaesthetic infusion. They were also asked to grade their pain care as poor, satisfactory, good or excellent.

4.2.3. Study III

Ninety patients with subacromial impingement disease undergoing shoulder arthroscopy were enrolled. The intra-articular assessment was carried out and subacromial decompression was performed. In the presence of associated rotator cuff tear, the torn tendon was attached to a footprint bone using titanium anchors. At the end of surgery, a surgeon inserted a catheter into subacromial space through an arthroscope, and the catheter was connected to a portable elastomeric infusion system (Two day Infusor, Baxter Healthcare Corporation). Continuous infusion using either bupivacaine, 5 mg/ml, or saline, 9 mg/ml, at a rate of 2 ml/h, was commenced immediately according to a randomisation. The duration of infusion was 48 hours.

The primary outcome was the consumption of oxycodone, and the secondary outcome pain score on NRS ranging from zero to ten. Pain assessments were recorded pre- and postoperatively, 6, 12, 18 hours after the beginning of operation and on the first and third postoperative day (POD). Patients were also asked about the possible adverse effects of local anaesthetic infusion (nausea, vomiting, tinnitus, visual disturbance, metallic taste, muscular twitching and/or muscular rigidity, dysarthria, cardiac arrhythmia, dizziness and perioral numbness) and the worst pain (the highest pain scores) at home.

Patients were discharged as outpatient if possible and they were instructed to remove the catheter on the second postoperative day at home.

4.2.4. Study IV

The study included 60 patients with rotator cuff disease scheduled for shoulder arthroscopy. All the patients received either a fentanyl 12 µg/h or placebo patch one hour before surgery. During surgery a general arthroscopic assessment of the glenohumeral joint was carried out. An acromioplasty or rotator cuff repair was performed. The surgeon placed a multi-orifice epidural 20-gauge catheter into the subacromial space under direct arthroscopic visualisation to ensure an accurate extra-articular placement. The catheter was connected to a portable elastomeric infusion system (Multirate Infusor, Baxter Healthcare), with a reservoir of 300 ml. Patients with a fentanyl patch received subacromial saline infusion and patients with a placebo patch had a bupivacaine 2.5 mg/ml infusion, and both infusions ran at a constant rate of 4 ml. Both the duration of the patch and infusion was 72 hours.

Pain scores on the NRS, the primary outcome measure, were asked through the whole follow-up period until the 90th postoperative day. Pain assessments were recorded pre- and postoperatively, at 6, 12 and 18 hours after the placement of the patch, on the 1st, 2nd, 3rd, 15th, 20th, 60th and 90th postoperative day. Also the highest pain scores (the worst pain) were recorded. At the same time points of pain assessment patients were interviewed about adverse effects (nausea, somnolence, itching, obstipation) until the 15th postoperative day. Opioid consumption was recorded on a daily basis.

All the patients stayed overnight at hospital. The patients were instructed to remove the catheter and the patch by themselves at home 72 hours after the operation.

On the 90th POD, patients were asked about their opinion of pain management, and their global impression of the impact of the surgery to overall quality of life. This was ranked on a scale from one to five: 1=change for much worse, 2=change little worse, 3=no change, 4=change for little better, and 5=change for much better.

4.2.5. Study V

Sixty in- or outpatients undergoing unilateral hallux valgus or hallux rigidus surgery were included. One hour before surgery a fentanyl patch 12 µg/h or a placebo patch was placed on patients' skin according to randomisation. Spinal anaesthesia was induced with 1.5 ml (7.5 mg) of hyperbaric bupivacaine. Prophylactic antiemetic, dexamethasone 5 mg, was given intravenously in anaesthesia induction. Intraoperatively no sedatives were routinely administered, but if requested, propofol was administered in 10-20 mg boluses. In hallux valgus cases, distal Chevron osteotomy or Lapidus procedure was performed. In hallux rigidus cases, cheilectomy of the first MTP I joint or MTP I arthrodesis was used.

The consumption of oxycodone was the primary outcome, and pain on NRS was the secondary outcome. The time points of evaluation were one hour preoperatively, right after surgery, at 6, 12, 18 hours after placing the patch, on the 1st and the 4th POD. Possible adverse effects such as somnolence, nausea, itching, obstipation as well as respiratory rate were recorded using numerical rating scale at the same time points. When at home, patients were also asked to register their pain scores, the worst pain (the highest pain scores), analgesic consumption and adverse effects.

Patients were discharged as outpatients if possible. They were instructed to remove the patch on the 3rd POD. A telephone interview was made by the investigator on the first and/or the fourth postoperative day.

4.3. Statistical analysis

In prospective power analysis, the α -level was 0.05 in all studies, as β -power of 0.9 was used in Studies I, IV and V and 0.8 in Studies II and III. In Study I, The calculation of the number of patients required was based on the studies of Kuusniemi and colleagues. According to power analysis 30 patients per groups would provide a power of 0.9 for detection of a 40-min difference in time to full motor block recovery. A difference of 40 min between groups with complete regression of motor block was assumed to be clinically relevant. In Study II, we calculated on a basis of previous studies that seven patients per group would be required to demonstrate that the total plasma bupivacaine concentration in the group receiving bupivacaine 5.0 mg/ml is 50 % smaller than the concentration of 2 mg/ml. To prepare for possible dropouts, eight patients were recruited into the both groups. In Study III, the power analysis showed that a sample size of 45 patients per group was required to detect a 30% difference in

opioid use between the groups. The mean daily use of opioids in patients receiving saline 60 mg and standard deviation (SD) 30 mg was taken from our previous pilot study. In Study IV, the prospective power analysis showed that 28 subjects per group were required to detect a 1.3-point mean difference in pain scores between the groups. A SD of 1.5 was based on the previous study evaluating the use of transdermal fentanyl for orthopaedic surgery (Van Bastelaere et al. 1995). To compensate for possible dropouts, we decided to recruit 30 patients per group. In Study V, the prospective power analysis showed that 30 patients per group would be required to show 50 % difference in rescue medication (oxycodone) use between the groups. A SD 22 and a mean total oxycodone consumption 19 mg (on the day of surgery and the 1st POD) were taken from our pilot study, in which the patients had a patch relieving fentanyl 12 µg/h. We estimated that patients having a placebo patch would need twice as much oxycodone as patients having a fentanyl patch, approximately 38 mg.

Differences between the study groups in normally distributed continuous variables were analyzed using an independent-samples t-test. In the case of non-normally distributed variables, a Mann-Whitney U test was used. Categorical variables were analysed using a Chi-Square test or Fisher's exact test. If the interaction of time and group was significant in the analysis, the difference between groups was tested separately at each time point. If there were more than three different doses of medicine used, analyses were performed using Mann-Whitney U-test, and in case of three or less doses, Fisher's exact test was used.

In Study I, physical characteristics, systolic and diastolic blood pressure, heart rate, the duration of motor block and recovery times were analyzed using one-way analysis of variance. The magnitude of motor block, medians of upper sensory limits and the sum of VAS results were analyzed by the Mann-Whitney rank sum test. The number of patients with VAS differing from zero, and that of patients needing circulatory or pain medication were analysed by the Fisher's exact test.

In Study II, bupivacaine, 4-OHB, DBB, AAG, pain scores and ECG variables, in Study III, pain scores, in Study IV, pain scores, scores of worst pain and somnolence, in Study V, pain scores and respiratory rates were analyzed using repeated measurements analysis of variance (rmANOVA). The response was square transformed to attain normality, thus medians were reported instead of means. The Bonferroni method was used to adjust the p-values of pairwise comparisons. Residuals were evaluated for justification of the analysis. p-values less than 0.05 were considered as statistically significant. Statistical analyses of studies II-V were carried out using SAS system for Windows, Version 9.2 (SAS Institute Inc, Cary, NC, USA).

5. RESULTS

5.1. Effects of intrathecal clonidine

Unilateral block was achieved using the addition of small-dose clonidine. The motor block was significantly different between surgical and contralateral sides in both groups at all testing times. A complete unilateral block was achieved in 73 % (22/30) of the patients in the bupivacaine-clonidine group (Group B-C) and in 77 % (23/30) in bupivacaine group (Group B). The addition of 15 µg clonidine into 5 mg bupivacaine prolonged the motor block (Fig. 4).

The sensory block spread higher in Group B compared with Group B-C. There was no difference in pain scores but there was a trend showing lower pain scores in Group B-C. The discharge of three patients in Group B was delayed because of pain.

Time to walking was 44 minutes longer in Group B-C (median 235 min, range 164-466 min) than in Group B (median 207 min, range 136-283 min) ($p < 0.001$), which was statistically significant different. However, there was no significant difference between the times to voiding (246 vs. 222 min) ($p < 0.068$) or between home-readiness (241 vs. 221 min) ($p < 0.258$).

Six patients in Group B-C needed etilefrine during the operation compared to none in Group B. Though no vasopressors were needed later on, after 1 hour and 45 minutes, the blood pressure differed statistically significantly with a decrease in Group B-C (Fig. 5).

Patients were satisfied with anaesthesia. Ninety per cent of the patients in group B-C and 78 % in group B considered anaesthesia perfect or adequate. The difference was not significant. Neither was there any difference in the opinion of the surgeon. All except one patient were willing to choose the same anaesthesia for a similar procedure in future.

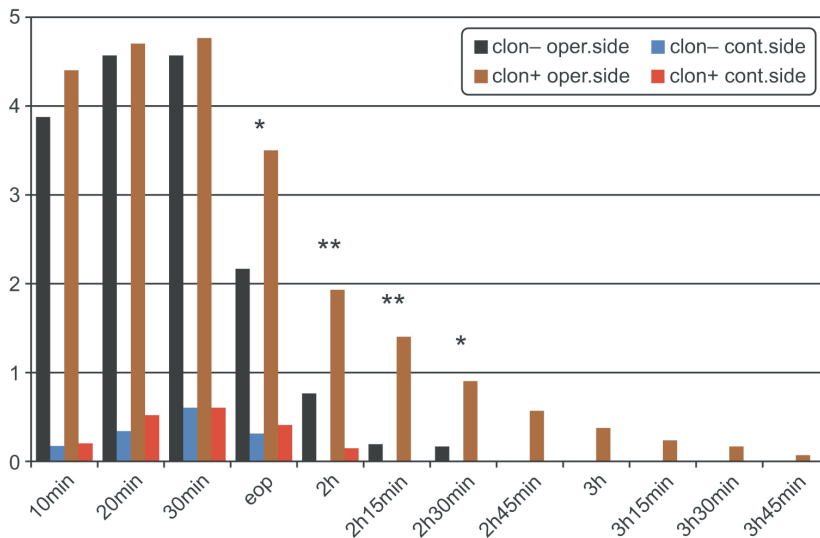


Figure 4. The total motor block score (modified Bromage scale from zero to five, values are mean) on the operated side and contralateral side (Merivirta et al. 2009). * $p < 0.05$, ** $p < 0.01$.

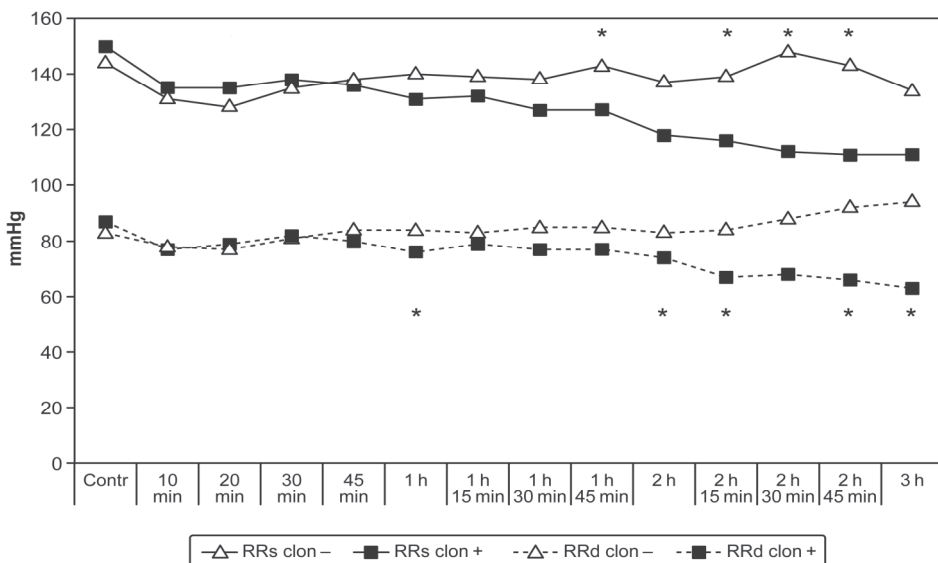


Figure 5. Systolic and diastolic blood pressures (mean). * $p < 0.05$ between the groups.

5.2. Plasma levels of bupivacaine and its metabolites

The mean plasma bupivacaine concentration increased to 0.24 $\mu\text{g/ml}$, i.e. 30 % compared to baseline during the first six hours, in those receiving 2.5 mg/ml bupivacaine infusion (Group B2.5), whereas in those receiving 5.0 mg/ml bupivacaine infusion (Group B5.0) the bupivacaine concentration increased about threefold up to 0.87 $\mu\text{g/ml}$ in 47 hours (Fig.6). The mean bupivacaine concentration was 0.24 $\mu\text{g/ml}$

(SD 0.1) in Group B2.5 and 0.87 $\mu\text{g/ml}$ (SD 0.30) after 48 hours continuous subacromial infusion and the difference was significant ($p=0.021$). The highest individual concentration was 1.26 $\mu\text{g/ml}$ in Group B5.0 at 48 hours. At that time point, the lowest concentration was 0.14 $\mu\text{g/ml}$ in Group B2.5.

The concentrations of two metabolites of bupivacaine also differed significantly between the groups at 48 hours. The highest mean concentrations of 4-OHB and DBB were 0.11 (SD 0.038) $\mu\text{g/ml}$ and 0.22 (SD 0.10) $\mu\text{g/ml}$, respectively, in Group B5.0.

There were no significant differences in pain scores or in morphine consumption.

Adverse effects, except nausea and dizziness, were infrequent as seen in Table 3. One patient had five symptoms during the first 24 hours and none during the following 24 hours. Two patients had no symptoms at any time and four patients only during the first 24 hours. All patients considered pain care to be good or excellent at 48 hours.

Between 24 and 48 hours, the AAG concentration rose significantly in both groups (Fig.6).

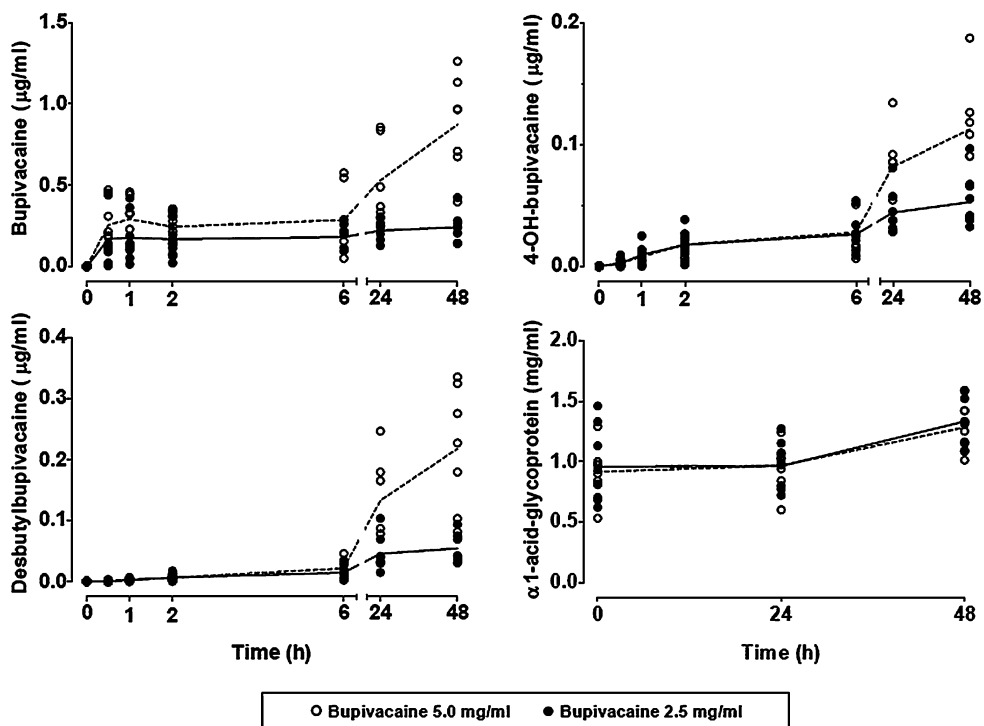


Figure 6. The mean and individual total plasma bupivacaine, 4-hydroxybupivacaine and desbutylbupivacaine concentrations over time. The continuous line is for mean plasma concentrations in Group B2.5 and the dotted line is for Group B5.0.

Table 3. Adverse effects on the patients with subacromial bupivacaine 2.5 mg/ml and 5.0 mg/ml during the first 48 hours (Study III)

	0-24 h		25-48 h	
	B2.5	B5.0	B2.5	B5.0
Nausea	5	5	2	2
Vomiting	1	1	2	-
Tinnitus	1	1	1	-
Visual disturbance	2	-	-	-
Metallic taste	-	-	-	-
Muscular twitching	1	-	1	1
Dysarthria	1	1	-	-
Dizziness	5	4	1	2
Arrhythmia/palpitation	-	1	-	1
Perioral numbness	-	-	-	-
Muscular rigidity	-	-	-	-

5.3. Analgesic effect of subacromial bupivacaine

Patients receiving subacromial bupivacaine infusion needed less oxycodone during the infusion compared to those receiving saline infusion. They also used less paracetamol on the day of surgery ($p=0.009$).

Pain scores were at their highest immediately after surgery (Fig. 7). Pain was experienced less in the bupivacaine group at 18 hours ($p=0.008$), which in most cases was night time. The worst postoperative pain at home did not differ between the groups ($p=0.058$) (Fig. 8).

There was no significant difference in adverse effects between the groups. Dizziness and nausea were the most reported adverse effects in both groups.

The duration of surgery was longer in the saline group (median: 76 min, range: 27-164 min) than in bupivacaine group (56 min, 27-167 min) ($p<0.05$), and rotator cuff – procedures were more frequent in saline group though this difference was not significant.

Table 4. Rescue oxycodone use (mg) (the modified table of Merivirta et al. 2012)

	Bupivacaine	Saline
In recovery room (<i>iv</i>)	10.0 (4.0-43.0)	16.0 (4.0-50.0)
Total amount on the operation day (<i>iv</i>)	15.0 (4.0-65.5)	20.0 (4.0-70.0)
On the 1 st POD (<i>po</i>)	0.0 (0.0-35.0)	10.0 (0.0-121.0)
On the 2 nd POD (<i>po</i>)	0.0 (0.0- 20.0)	0.0 (0.0-20.0)
On the 3 rd POD (<i>po</i>)	0.0 (0.0-10.0)	0.0 (0.0-10.0)

Numbers are median (range)

5.4. Transdermal fentanyl as a part of multimodal analgesia

5.4.1. The effects of transdermal fentanyl after shoulder arthroscopy

There was no significant difference in pain scores (Figure 7 and 8) or opioid consumption (Table 5) between the patients receiving bupivacaine infusion and those having a fentanyl patch.

The most common adverse effect, nausea, was most reported immediately after surgery. Later on, 0-2 patients in both groups expressed the nausea as 1-4 points out of ten. One patient in fentanyl group discontinued the study because of severe nausea. Except immediately after surgery, the given scores (median) for somnolence were from 2-6, and starting from the 1st POD the scores were zero. Postoperative itching was rated mild with 1-3 on the NRS. Eight patients with a fentanyl patch and six with a placebo patch expressed that when inquired. Constipation was reported by 4-5 patients in both groups. Respiratory rates (median) varied between 12-15 and did not differ between the groups.

The satisfaction to pain care or global impression of the impact of the surgery on the overall quality of life did not differ between the groups. Nine patients in the fentanyl and 10 in the bupivacaine group considered the change of overall quality of life after surgery much better, 8 and 7, respectively of each group, a little better. Four patients in both groups reported no changes. Altogether 5 patients considered the change worse or much worse.

Table 5. Rescue oxycodone use (mg) (the modified table of Merivirta et al. 2013)

	Fentanyl	Bupivacaine
In recovery room on the day of surgery (<i>iv</i>)	15 (0-40)	13.5 (3-36)
In the ward on the day of surgery (<i>iv</i>)	0 (0-6)	0 (0-6)
On the 1 st POD (<i>iv</i>)	0 (0-9)	0 (0-9)
On the 1 st POD (<i>po</i>)	0 (0-30)	0 (0-40)
On the 2 nd POD (<i>po</i>)	0 (0-20)	0 (0-10)
On the 3 rd POD (<i>po</i>)	0 (0-10)	0 (0-10)

Numbers are median (range)

5.4.2. The effects of transdermal fentanyl after forefoot surgery

The need of rescue oxycodone was low both in fentanyl and placebo group, and did not differ significantly between them (Table 6). Thirty-six percent wearing a fentanyl patch and 25 % wearing a placebo patch did not need rescue analgesic on the day of surgery. On the 1st POD, 70 % and 73 %, respectively, managed without rescue opioid.

Pain scores are seen in Figure 7 and 8. There were no statistically significant differences between the groups.

Ten patients with a fentanyl and eight with a placebo patch reported nausea. The experienced nausea was mild, 1-3 on the NRS, with two exceptions, and in most of cases it was disappeared until the next timepoint. One patient in the fentanyl group discontinued the study because of severe nausea. The scores of somnolence (median) varied from 1-2 on the NRS. Itching was not reported without a specific question but when inquired a few patients rated it as 1-3 on the NRS in both groups. Constipation was reported by five patients in the fentanyl and one in the placebo group on the 4th POD. The respiratory rate (median) varied between 12-14/min during the 1st POD among those staying overnight at hospital. The lowest frequency, 8/min, was in the fentanyl group at 12 hours.

Table 6. Rescue oxycodone (mg) use in Study V (Merivirta et al.)

	Fentanyl	Placebo
On the operation day	10 (0-50)	10 (0-50)
On the 1 st POD	0 (0-20)	0 (0-20)
On the 2 nd POD	0 (0-35)	0 (0-10)
On the 3 rd POD	0 (0-0)	0 (0-0)
On the 4 th POD	0 (0-0)	0 (0-0)
Total opioid consumption during the study	10 (0-105)	20 (0-70)

Numbers are median (range)

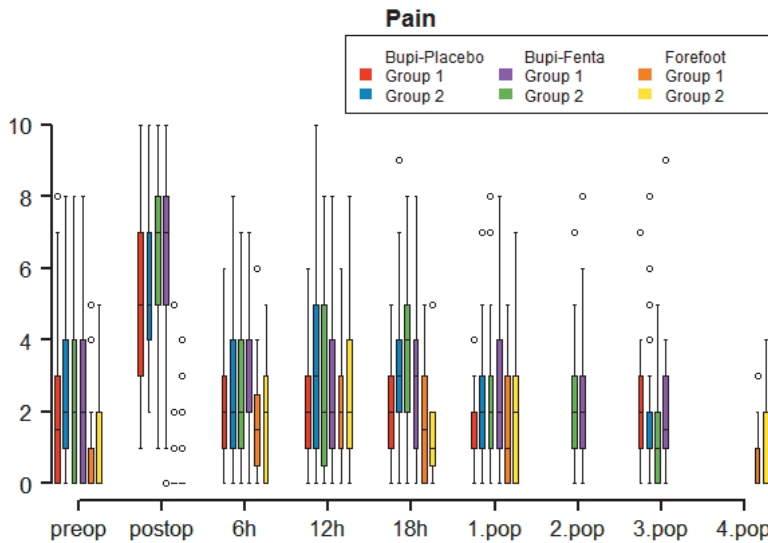


Figure 7. Pre- and postoperative pain scores in study groups. Bupi-Placebo (Study III): Group 1 is bupivacaine and Group 2 placebo group. Bupi-Fenta (Study IV): Group 1 is bupivacaine and Group 2 fentanyl group. Forefoot (Study V): Group 1 is fentanyl and Group 2 placebo group. The top and bottom of the boxes indicate the upper and lower quartiles, and the horizontal line in the box shows the median. Whiskers from the box indicate the most extreme point less than or equal to 1.5 interquartile ranges. Outliers (individual values >1.5 interquartile ranges) are shown with dots.

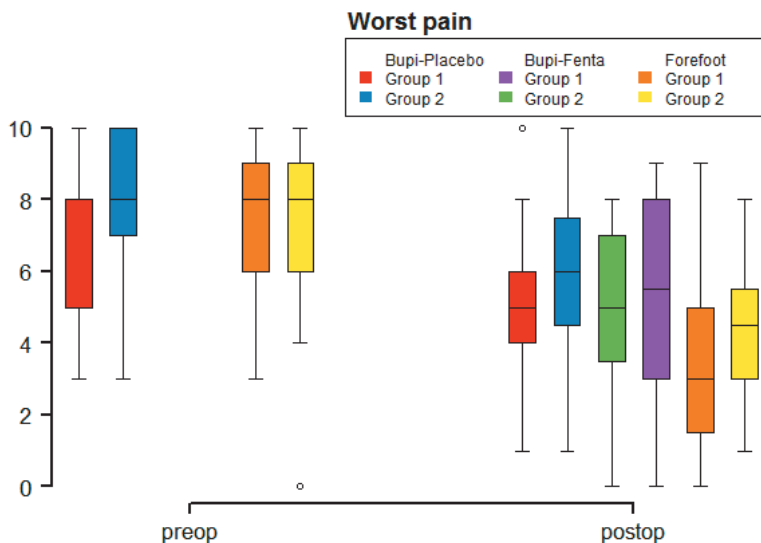


Figure 8. The highest pain scores preoperatively and after discharge until the 3rd or 4th postoperative day. Bupi-Placebo (Study III): Group 1 is bupivacaine and Group 2 placebo group. Bupi-Fenta (Study IV): Group 1 is bupivacaine and Group 2 fentanyl group. Forefoot (Study V): Group 1 is fentanyl and Group 2 placebo group. The top and bottom of the boxes indicate the upper and lower quartiles, and the horizontal line in the box shows the median. Whiskers from the box indicate the most extreme point less than or equal to 1.5 interquartile ranges. Outliers (individual values >1.5 interquartile ranges) are shown with dots.

6. DISCUSSION

6.1. Pain and pain scores

The purpose of our studies was to evaluate the effectiveness of certain pain modalities in patients scheduled for day surgery. There is evidence that pain is still undertreated also in day surgery (Gerbershagen et al. 2013). However, the major finding based on the present studies was generally lower pain scores than expected. If the immediate postoperative phase and at 18 hours the shoulder group having a fentanyl patch in Study IV were ruled out, median pain scores at all used time points was recorded mild ($\text{NRS} \leq 3$) in shoulder and forefoot studies. All the groups reached median pain scores of two or below on the 1st POD, and already in a couple of days, pain was weakened to a preoperative level. Similar findings were made by Stiglitz et al., who showed the mean VAS maintained under four, and concluded that shoulder arthroscopy produces less pain than earlier reported (Stiglitz et al. 2011). A $\text{NRS} \geq 4$ has been identified to be a threshold in the study for determining the cut point from mild to moderate-to-severe pain postoperatively (Gerbershagen et al. 2011). The same score was considered as a threshold for tolerable pain by patients themselves already in the preoperative phase.

The highest median pain scores representing the worst pain experienced at home, in our studies were ≤ 6 on the NRS and this indicates moderate pain (based on a previous study: Cepeda et al. 2003). Despite of that, there were still a few patients experiencing the worst pain imaginable (pain scores 10 on NRS). Unfortunately, we did not ask the worst pain during the hospital stay. Neither did we scrutinise the patients who reported the highest pain scores afterwards to find out possible reasons, nor predictive factors for severe pain.

Based on earlier studies considering 1.3 units on the NRS as the minimal improvement in moderate pain (Cepeda et al. 2003) and 1.4 on the VAS as the minimal clinically important difference (MCID) in patients having rotator cuff tear (Tashjian et al. 2009), we chose the difference of 1.3 between the groups for power analysis in our Study IV. In severe pain, the change should be larger, i.e. 1.8 for minimal improvement (Cepeda et al. 2003). Though pain scores were assessed in the immediate postoperative phase, patients were not categorized according their pain intensity. Therefore the patients in moderate or severe pain may have benefited more from the used pain modality than those in mild pain (Breivik et al. 2008). The median pain scores reduced from five and seven in the immediate postoperative phase to two at 6 h in Studies III and IV. That means a 60-70 % reduction in pain scores. These reductions measured both in pain scores and percentages correlate with a clinical meaningful pain relief (much improvement) which has been identified to be 2.4 (35 %) in moderate pain and 4.0 (44 %) in severe pain (Cepeda et al. 2003).

Though pain experience and rating are very subjective, pain scales are useful tools in following the pain of the patients over time. Their use also facilitates the understanding

of postoperative pain and evaluation of pain treatment by healthcare professionals (Wikström et al. 2014). NRS and VAS are valid and reliable in routine clinical assessment but NRS is more practical (Breivik et al. 2008). We chose to use NRS in all other studies except in Study I, because of its suitability for telephone interviews. As many things, like the habits of health care professionals, have effects on interpretation of pain (Wikström et al. 2014), and because of the varying correspondence between difference scales (Dijkers 2010), it is important to use the same scale and questions consistently. Before using a scale, the patient's ability and understanding to express their pain on a scale have to be assured. When assessing pain in orthopaedic patients not only pain at rest but also pain in movement, is essential to record to ensure adequate pain relief for early mobilization and rehabilitation.

In our studies, we evaluated pain scores, consumption of analgesics and adverse effects. In studies I, II and IV patient satisfaction with anaesthesia and/or pain management were assessed despite of the fact that patient satisfaction with pain management does not automatically correlate with pain scores or with the changes of the scores (Kelly 2000). Overall satisfaction after day surgery is high. Over 95 % of outpatients are satisfied but postoperative pain has an impact on overall satisfaction (Lemos et al. 2009).

6.2. The use of rescue opioid

The opioid consumption in our studies was moderate on the day of surgery and modest thereafter. Nevertheless, there were single patients who needed large doses of rescue opioid at some point, despite of our multimodal analgesia protocol. However, a considerable need for rescue opioid for these patients was generally limited to the day of surgery and/or the 1st postoperative day. Interestingly, the shoulder patient, who needed the largest amount rescue opioid (121 mg oxycodone *po*) on the 1st POD, needed no oxycodone on the 2nd POD.

Rescue opioid use may depend not only on pain severity but also willingness to use opioids, metabolism of opioids as well as tolerance for possible adverse effects (Mc Lean 2013). As seen in these and other studies, patients do not always ask for analgesics or take them even when they have pain (Beauregard et al. 1998, Maroney et al. 2004, Wilson et al. 2004). There may be a discrepancy between reported and accepted pain, as seen in the study of Maroney et al., where 31 % of the patients experiencing severe pain still reported it to be acceptable (Maroney et al. 2004). Reasons for this were resolved pain, beliefs that it would disappear or that no additional pain relief would be feasible, good tolerability and stoic attitude. In their study, five percent of the patients simply did not want to take analgesics and one percent feared adverse effects. Though these findings were made amongst hospitalized patients, similar findings have been made among outpatients (Beauregard et al. 1998). This was also seen in our studies as some patients preferred not to use rescue opioid at home even when reporting pain.

6.3. The role of multimodal analgesia

The aim of multimodal analgesia is to improve effectiveness and safety of pain management, as well as to reduce opioid use and adverse effects related to it. In our studies we used multimodal analgesia consisting of regular paracetamol and/or ibuprofen, a studied method and rescue oxycodone. Barber et al. administered subacromial bupivacaine infusion at 10 mg/h, the same dose as we used, but they used no other regular analgesia during the infusion (Barber et al. 2002). Mean pain scores of near six on the 2nd POD indicated moderate pain contrary to mild pain of our patients with regular background analgesics. As the median pain scores, in our study, were generally low, the use of background analgesia, paracetamol and ibuprofen, may have covered or decreased a possible difference in pain scores between the groups. Multimodal analgesia is, however, the standard care in day surgery.

Launching the term “procedure-specific approach”, White and Kehlet wanted to remind clinicians about wide scale of surgical procedures with unique characteristics (Kehlet et al. 2007, White et al. 2010). They recommended these attributes should be considered together with other surgical issues in order to enhance the recovery and rehabilitation when analgesics are prescribed. Day surgery consists of different types of surgical procedures and therefore, there cannot be universal guidelines for postoperative pain management. In our studies, we concentrated on the certain procedures with the specific methods, like subacromial bupivacaine, with the intention of finding the best possible pain modality or a good alternative to the modality in use. Alternatives enable also a patient-specific approach. All the used methods in our studies allowed fast recovery and discharge with acceptable adverse effects, if three patients with severe nausea in fentanyl groups were excluded.

6.4. Unilateral spinal block and clonidine

Using 15 µg of clonidine as an adjunct together with low-dose bupivacaine, we were able to reach complete unilateral spinal anaesthesia in 73 % of cases. As expected, clonidine prolonged the motor block, which is in accordance with the study of van Tuijl where they used the same combination of clonidine and bupivacaine as we did (van Tuijl et al. 2008). Also time to voiding was prolonged but not statistically significantly in neither study. The difference was approximately 20 minutes, which may have some clinical significance by affecting discharge times. In our study, as also in van Tuijl's, one of the discharge criteria was ability to void spontaneously despite the recommendation to exclude this criterion if a procedure is not hernia repair, urological or rectal procedure (Mulroy et al. 2002). Nowadays, voiding is not required when discharged from the Surgical Hospital in Turku.

Clonidine has analgetic effect and improves anaesthesia as seen in patients' reduced need for analgesic or anaesthesia and/or reduction of pain scores in children and adults (De Kock et al. 2001, Laisalmi et al. 2001, Dobrydnjov et al. 2003, Kaabachi et al. 2007, van Tuijl et al. 2008). In our study, only a tendency of less pain was seen. The pain scores were very low in both groups, which may explain the finding that no

significant difference was seen. However, the discharge of three patients was delayed because of pain in the plain bupivacaine group.

Despite of a unilateral block, a clonidine dose as small as 15 µg in combination with low-dose bupivacaine induced the use of vasopressors in the beginning of the block in 20 % of our patients. According to the meta-analysis of Elia et al., hypotension caused by clonidine is not dose-dependent (Elia et al. 2008). However, most of the studies included in the analysis used 15 mg or more of bupivacaine, which probably have covered the effect of clonidine on blood pressure. When different doses of clonidine were used with low-dose ropivacaine, a dose dependent reduction in blood pressure has been reported (De Kock et al. 2001). The addition of a clonidine dose of 45 or 75 µg caused hypotension, in contrast to a dose of 15 µg in their work

The well-described method for performing unilateral block is injecting low dose of hyperbaric bupivacaine through a pencil-point needle while the patient is in the lateral position, operative side dependent, for 15 minutes (Casati et al. 1999, Borghi et al. 2003). We used the same method to achieve unilateral spinal anaesthesia in our study, but instead of 15 minutes in lateral position, we chose 10 minutes, which has been shown to be sufficient time to produce surgical block when hyperbaric bupivacaine 6 mg has been used (Borghi et al. 2003). We also used a pencil-point needle but rather because of lower incidence of post-dural puncture headache (Halpern et al. 1994) than its relevance to unilaterality. In fact, needle type has no effect on achieving the unilateral motor block (Casati et al. 1998, Kuusniemi et al. 2013).

6.5. The safety and efficacy of subacromial bupivacaine infusion on pain in shoulder arthroscopy

6.5.1. The safety of subacromial bupivacaine

In Study II, the total plasma concentrations of bupivacaine and its metabolites were determined after a subacromial initial bolus and infusion of bupivacaine in two different concentrations. As the site of injection affects absorption rate (Tucker et al. 1979), the doses of local anaesthetics should be based on site and specific block in addition to individual characteristics rather than standard doses (Rosenberg et al. 2004). The highest mean venous plasma bupivacaine concentration, 0.87 µg/ml, in our study stayed below toxic level, which has been considered to be in the range from 2 to 4 µg/ml (Wiklund et al. 1977, Mather et al 1979). These concentrations were measured from arterial blood, where concentrations are twice as high as venous values in the early phase (Tucker et al. 1979, Knudsen et al. 1997) but during the extravasal infusion of bupivacaine the differences are almost identical (Chiou 1989). The maximum tolerated mean (range) concentration in venous plasma *iv*-infusion of bupivacaine has been reported to be 2.1 µg/ml (0.8-4.5) (Knudsen et al. 1997). The most common symptoms occurring during bupivacaine intravenous infusion were visual and hearing disturbances, perioral numbness, tinglins, paraesthesia, dysarthria, dizziness and muscular twitching (Knudsen et al. 1997). The highest individual concentration in our study was 1.26 µg/ml, still below these toxic levels. There were some patients

experiencing subjective adverse effects similar to the symptoms occurring in the study of Knudsen et al. As nausea and dizziness, the most common adverse effects in Study II, were relieved after terminating the morphine-PCA, we considered morphine to be an explanation to them. The measured bupivacaine concentrations were not, however, related these adverse effects. The patient with the highest concentration had nausea and dizziness on the day of surgery but no symptoms after that. The patient reporting visual disturbance, muscular twitching, dysarthria, dizziness and also symptoms outside of the inquired ones during the first 24 hours, had the bupivacaine concentration of 0.13 at 24 h. When bupivacaine infusion of 10 mg/h was compared to saline infusion, patients experienced adverse effects in both groups. However, single patients only in bupivacaine group reported perioral numbness, visual disturbance and dysarthria. Therefore, we cannot totally exclude the possibility of toxicity. Anyhow, patients did not report adverse effects spontaneously, except nausea and vomiting. We can presume that other adverse effects cause only minor discomfort because specific questioning was needed to reveal them.

Also, the concentrations of metabolites: desbutylbupivacaine and 4-OH-bupivacaine increased during the bupivacaine infusion. Their highest mean plasma concentrations were 0.22 (range 0.031-0.34) and 0.11 (range 0.032-0.19) µg/ml, respectively. After continuous interscalene brachial plexus block, the concentrations have been 0.33 and 0.13 µg/ml (Rosenberg et al. 1991). As the cardiac toxicity of DBB is approximately half of that of bupivacaine and CNS toxicity even less (Rosenberg et al. 1992), it seems that determining the concentrations of these metabolites is more due to an academic interest than a real clinical significance.

An increase in AAG after surgery was seen in our study in line with other studies (Aronsen et al. 1972, Rosenberg et al. 1991, Veering et al. 2002). The increase was not yet seen at 24 hours but at 48 hours. This is accordance with the study of Veering et al (Veering et al. 2002) but opposite to the study of Aronsen et al, who noticed apparent rise within 24 hours (Aronsen et al. 1972). AAG is the major binding protein for bupivacaine and sensitive to surgery and trauma. The increase of AAG explains, why the unbound plasma bupivacaine concentration, the active portion responsible for toxicity, is not increased in proportion to total plasma concentrations but reaches a plateau between 12 to 24 hours after infusion (Veering et al. 2002). We did not determine the unbound bupivacaine concentrations but total plasma concentrations that can be considered as a weakness of this study.

Intra-articular bupivacaine infusion has been related to chondrotoxicity. Therefore, the catheters in our study were placed subacromially under direct visualization, thus minimizing that risk. However, there may still exist some leakage into the intra-articular space even after an adequate repair. We did not take any routine imaging postoperatively but there were no clinical signs of chondrolysis during the 90 postoperative days.

6.5.2. The efficacy of subacromial bupivacaine

When subacromial bupivacaine infusion was compared with saline infusion, rescue opioid was used less in patients having bupivacaine infusion during the 48 hours

postoperative infusion. Median pain scores differed only at 18 hours (during the nighttime). This is most probably explained by irregular nighttime administration of other analgesics but bupivacaine infusion offered background analgesia, which reduced pain scores at the time. Overall consumption of rescue opioid on the day of surgery was quite low, 15 and 20 mg (median) intravenously in bupivacaine and saline group. Because no initial bolus of bupivacaine into subacromial space was used and the onset of bupivacaine infusion is slow, the maximum pain scores (median) were measured at immediate postoperative phase. The highest pain at home, inquired on the 3rd POD, was reported as moderate.

These results are in line with previous studies showing that the effectiveness of continuous subacromial local anaesthetic (Savoie et al. 2000, Barber et al. 2002, Coghlan et al. 2009). However, we considered this statistically significant difference in rescue opioid consumption between the groups, clinically insignificant. In fact, Coghlan et al reached the same conclusion in their trial evaluating the effectiveness of subacromial ropivacaine infusion (Coghlan et al. 2009). In their study, there was a statistically significant difference in pain scores between ropivacaine and placebo group during the first 12 hours and in opioid consumption during the second 12 hours. They considered the difference of 0.7 (mean) in pain, measured using the NRS, and 2.47 mg (mean) in opioid consumption clinically insignificant. In our study, the difference in opioid consumption (median) was 5 mg oxycodone *iv* on the day of surgery and 10 mg oxycodone *po* on the 1st postoperative day. The widest difference in pain scores was one on NRS, which is less than MCID in rotator cuff patients. Furthermore, there were some technical problems hampering this pain modality: one detached catheter and two cases of obvious catheter and/or pump dysfunction in our study. Coghlan et al. noticed a great variation in the rate of delivery of the infusion. In the majority of cases, the infusion rate was greater than programmed (Coghlan et al. 2009). We did not check the pumps or asked about them specifically from discharge patients. This may have revealed the same problem. However, there were two pumps not deflating properly leading to exclusion of these patients. Unexpected flow rates have also been reported by others (Ackermann et al. 2007, Remerand et al. 2008) as well as dysfunctional pumps (Remerand et al. 2008).

Due to the clinically insignificant benefits of subacromial bupivacaine infusion, we abandoned the continuous subacromial local anaesthetic technique as a routine in pain management of shoulder patients at the Surgical Hospital in Turku. Considering the low need of opioids, expenses and technical failures, subacromial bupivacaine infusion conferred only moderate and clinically insignificant efficacy compared to placebo. Subacromial bupivacaine infusion has been replaced by a single shot supraclavicular block. Also the introduction of ultrasound devices enhanced the change. At the same time with our study, the MUMM-review about continuous wound infusions of local anaesthetic was published (MUMM-review 2011). Though subacromial local anaesthetic infusion is not technically a wound catheter, the MUMM-recommendation covered also that. Also their conclusion stated that the present evidence of the efficacy of wound catheters do not support routine use.

6.6. The effectiveness of transdermal fentanyl

6.6.1. In shoulder arthroscopy

Similarly to subacromial bupivacaine infusion, transdermal fentanyl offers effective background analgesia without the need for *iv*-access or capability to take analgesics per mouth. There were no significant differences in pain or rescue opioid consumption between those having a fentanyl patch and subacromial bupivacaine infusion. After the first postoperative day, more than half of the patients managed without any rescue opioid most probably due to these background analgesics. However, both transdermal fentanyl, as well as subacromial bupivacaine infusion with no initial bolus, has a delay in reaching the effective plasma drug concentrations and other pain modalities are needed during that time. Because of this delay, patients, in our study, experienced maximum pain during the immediate postoperative phase. In the literature, the mean delay time to minimum effective concentration of fentanyl in abdominal surgery patients has been reported to be approximately 11 to 13 hours if patches delivering fentanyl 50-125 µg/h have been used (Gourlay et al. 1989, Siafaka et al. 2004) but indeed, the MEC of transdermal fentanyl depends on the intensity and duration of pain, therefore the delay time to reach MEC may vary depending on procedures. As one solution to this delayed onset time, fentanyl patches have been applied hours before surgery (Minville et al. 2007) but due to a nature of day surgery this is not possible. Also, the safety of applying a fentanyl patch to an opioid naïve patient at home before a pain stimulus can be questioned.

Our patients having transdermal fentanyl did not have more adverse effects compared with those having bupivacaine infusion. Though the incidence of nausea was low in both groups, it seemed to be more severe among the patients wearing a fentanyl patch, as one patient wanted to discontinue the study and the other patient needed three times antiemetics. In other studies, the incidence of nausea has been greater but not necessarily different from placebo group (Van Bastelaere et al. 1995, Sevarino et al. 1997, Reinhart et al. 1997). This can be explained by general anaesthesia with nitrous oxide and other inhalational gases and by postoperative morphine use. Studies reporting more nausea or vomiting in fentanyl groups compared with placebo have used six to eight times larger doses of fentanyl than we did (Caplan et al. 1989, Lehmann et al. 1997). The small dose of fentanyl we used, and presumably low plasma concentration, also explains the fact we did not observe bradypnoea or sedation, contrary to some other reports (Reinhart et al. 1997) where even naloxone has been required to antagonise the side effects (Sandier et al. 1994).

One deficiency in the use of transdermal fentanyl is the impossibility of dose titrating. Our aim was, however, to find an effective and safe alternative background analgesia about which a fentanyl patch 12 µg/h was able to fulfil. As supraclavicular block has now gained popularity, transdermal fentanyl could be combined with it to achieve immediate effective pain relief by the block and continued by transdermal fentanyl. This might resolve the problem of pain caused by delay time of transdermal fentanyl, and it might have an effect on rebound phenomenon after perineural block. However, if

subacromial bupivacaine has been used after interscalene block, it has not totally prevented the phenomenon (DeMarco et al. 2011).

6.6.2. In forefoot surgery

In the comparison between transdermal fentanyl, 12 µg/h, and placebo after hallux valgus or hallux rigidus procedure, no significant difference in rescue opioid consumption or pain scores was observed. Two explanations can be offered for this. Firstly, we used multimodal analgesia consisting of ibuprofen, paracetamol and a single dose dexamethasone, which are all known to be effective in relieving postoperative pain after orthopaedic procedures. The effectiveness of NSAIDs after orthopaedic surgery is marked (Arvidsson et al. 1987, Hoe-Hansen et al. 1999, Southworth et al. 2009). When comparing our study to the study of Mattila (Mattila et al. 2010), they used only paracetamol and dexamethasone for the first three postoperative days and no NSAIDs. The total rescue oxycodone consumption of their patients was 45 mg in dexamethasone and 75 mg in placebo group compared with 20 mg in placebo group of our study. Secondly, if the baseline pain is moderate, the minimal improvement in pain scores in NRS, noticed by patients, is 1.3, and greater in severe pain (Cepeda et al. 2003). To detect meaningful treatment effects, sufficient pain intensity is needed (Breivik et al. 2008) but in our study, baseline pain, measured after surgery, was even less than moderate, meaning pain scores were two or lower, which probably have hampered the identification of any further decline in pain scores. An analogous finding was used by Turan et al. studying the effect of ankle block after hallux valgus surgery (Turan et al. 2007). They added a single shot ankle block to multimodal analgesia with etoricoxib and paracetamol but found no significant effect for the need of rescue analgesia or pain during the first 24 postoperative hours. In another study of Turan, they reported that 34 % of hallux valgus patients managed with etoricoxib 120 mg per day, and 75 % managed without any opioids (Turan et al. 2008). Twenty-five percent of our patients in the placebo and 36 % in the fentanyl group needed no opioid on the day of surgery, and day after the percentages were 73 and 73, respectively. However, still 8 % of the patients experienced severe pain at some occasion in the study of Turan (Turan et al. 2008). Also we had patients reporting pain score of eight, and maximum total dose of rescue opioid during the study was 103 mg. Our range of forefoot procedures was wider, which can partly explain the differences in the need of rescue medication. Even though pain scores reported for the worst pain (median 3.5, range 0-7) by patients wearing a fentanyl patch tended to be a little less than in the placebo group (5, 1-8), the difference was not significant and generally, transdermal fentanyl had no major impact on pain or opioid consumption after hallux valgus and rigidus surgery.

A fentanyl patch did not increase adverse effects. This is in line with our study, evaluating the effectiveness of transdermal fentanyl after shoulder arthroscopy. There was no difference in the incidence of nausea, however, in those experiencing nausea it tended to be more severe in the fentanyl group leading to the discontinuation of the study by one patient.

6.7. Adherence to medication

A surprise of these studies was the independent way in which these patients used analgesics. The instructions were given verbally by a nurse and the investigator, as well as in written form. They were also written into the prescription. Despite all these instructions, many patients used ibuprofen and paracetamol more as on a required-basis than regularly. The use of paracetamol was even more irregular, perhaps because patients are aware of its mild effectiveness. When combination of paracetamol and codeine was prescribed (in Study III), some patients preferred it to ibuprofen. These same findings have also been made by others (Wilson et al. 2004). Another opposite astonishment was that some patients in moderate or severe pain had not utilized the rescue oxycodone given home but decided to manage without. Explanations given to this kind of acceptance are based on the beliefs and fears of patients. Patients believe that they will become addicted or that pain cannot be treated, they fear adverse effects of analgesics and are convinced that pain should be tolerated (Beauregard et al. 1998, Maroney et al. 2004).

The finding of low adherence to prescriptions has been reported for decades (Sackett 1979). This is the case also with the use of analgesics. Sixty-six percent of 10 000 electronical prescriptions for analgesics was ever filled, and from 3500 newer prescriptions only 45 %, even though non-adherence is more common in American studies than in other countries (Fischer et al. 2010).

In Study V, five patients from 60 were excluded because analgesic use outside of the protocol. One reason for this may be that the protocol for the four first postoperative day differed from the instructions given by a surgeon for following days. Nevertheless, some patients simply disregarded the given instructions.

6.8. Limitations of the studies and general discussion

It is worth questioning whether pain scores are the best primary outcome when two methods for pain management are compared. As patients should have an access to rescue medicine, they should also be sure to reach adequate pain relief. This means that no significant differences in pain scores are supposed to be found, contrary to the use of rescue analgesia. On the other hand, as discussed earlier rescue opioid use may depend on not only pain but also on many other things.

Nowadays, one essential end-point following day surgery is health-related quality of life (HRQoL) (Mattila et al. 2012) reflecting the recovery more accurately than bare pain assessment. We did not assess HRQoL. However, 12 weeks after shoulder arthroscopy the patients went to see a physiotherapist, who evaluated their physical function, the use of analgesics, the quality of sleep and return to work. Still no data concerning the emotional well-being and social functioning were registered.

Our use of bupivacaine for subacromial infusions can be criticized, as there are other effective but safer options like ropivacaine and levobupivacaine which both have less

toxic potential (Knudsen et al. 1997, Stewart et al. 2003, Casati et al. 2005). On the other hand, the risk of systemic toxicity with the used doses and infusion method is small. There are reports of chondral damage after intra-articular bupivacaine infusion (Anderson et al. 2010), and *in vitro* bupivacaine has been found more chondrotoxic than ropivacaine (Piper et al. 2008). As infection is another feared complication after shoulder surgery, the use of bupivacaine can be advocated by its clearly more significant antibacterial effect compared with ropivacaine (Pere et al. 1999). Moreover, at the time of these studies, the use of bupivacaine was routine in Turku University Hospital, and bupivacaine was infused subacromially not intra-articularly. Since then ropivacaine has substituted bupivacaine in central neuraxial and peripheral nerve blocks in Turku University Hospital.

The fact that the given instructions concerning the use of analgesics were met with such a poor adherence came as a surprise. There were many patients, who did not follow the study protocol closely. Some patients were excluded for this reason. We were not sufficiently prepared for these dropouts.

6.9. Future challenges of pain management in orthopaedic day surgery

Based on our studies, shoulder arthroscopy and forefoot surgery are generally experienced less painful than we are made to understand by many, although not all the other recent studies evaluating the pain of outpatients. Nevertheless, there were patients in severe pain, who needed large doses of opioids; this despite the fact that we had excluded the patients with known pain problems or chronic pain and also patients with psychiatric disorder like depression, which may predict more intense pain experience. The challenge lies in screening before surgery those patients, who are more sensitive to pain experience or who have a disorder in pain modulation, thus providing individual and sufficient pain management. Though there are known predictors for pain, it is not always obvious, who is at risk to experience severe pain; nor are current experimental pain testing methods suitable for routine, daily work, - even the correlation may be weak (Kaunisto et al. 2013) or even nil (Kim et al. 2004). Preoperative anxiety and pain catastrophizing, which are known to correlate with postoperative pain (Kaunisto et al. 2013), have shown only limited association to postoperative pain in outpatients (Gramke et al. 2009). If this is a consequence of outpatients' minor stress, it can be considered as one of the advantages of day surgery. Research work around genetic factors in pain modulation is eager. One object with large interest has been the influence of COMT genotype on pain ratings. However, a recent study failed to show an association between COMT variants and opioid consumption and questioned the clinical relevance of that gene (Kambur et al. 2013).

As the population in Western Countries ages, there is also an increasing number of elderly people needing surgical interventions. Elderly patients have more comorbidities (Chung et al 1999) and older age is a predictor for unplanned hospital admission (Mathis et al. 2013). These factors should be taken into consideration when planning the perioperative care of elderly outpatients. Age is not a contraindication for surgery as such, but elderly patients may require more individual management. Because of the

changes in pharmacokinetics due to aging, elderly patients need titrated doses of analgesics (Liukas et al. 2011, Liukas et al. 2011). Also the social environment, elderly outpatients' comprehension and acceptance may bring challenges. The benefits of day surgery, especially for the elderly, are a short separation from family and home or a familiar environment, which decreases the probability of confusion and delirium, a lower incidence for hospital infections and a reduced risk for immobilization (Bettelli 2010). Similarly, the number of obese patients is increasing. Though there are no weight limits for day surgery, morbid obesity demands a good evaluation of these patients and comorbidities to be made in advance. Due to OSA morbidly obese patients are frequently more sensitive for adverse effects of opioid. In order to avoid opioids, multimodal analgesia is important and regional analgesia is favoured, though it may be technically challenged (Alvarez et al. 2014). Because of the extended patient population, the need for pre-assessment can be expected to increase in order to avoid unexpected cancellations on the day of surgery. Though the aim in future is to further increase the number of outpatients and decrease the need of hospital beds, the possibility to stay overnight because of an unplanned admission or re-admission has to be considered when planning where to perform day surgery.

The types and complexity of surgical procedures performed on day basis expand all along, which can be a challenge for procedure-specific pain management. At the same time, when compared with conservative treatment, some procedures are found useless in the attempt to improve the wellbeing and physical function of the patients being therefore abandoned. There is already a need for individual pain management due to different issues, like allergies, liver and kidney diseases, coagulopathies, drug abuse etc. in addition to genetic variations in pain modulation and drug metabolism. Also the capability and willingness of the patients have to be taken into account when planning pain care. Furthermore, the medical staff should be aware of the different beliefs and expectations of the patients or their fear of adverse effects. The fact remains that the medicines are rarely used as prescribed, though the adherence rate is higher in acute conditions (Osterberg et al. 2005). Moreover, physicians are poor in estimating patient adherence (Osterberg et al. 2005). The complexity of the instructions or the pain management itself can reduce patient compliance and the effectiveness of the planned pain care. Written instructions, explaining the benefits of prescribed medicine and personal phone calls have improved adherence for short-termed drug treatments (Haynes et al. 2009).

The mobilization of the patients is crucial for prompt discharge, especially after orthopaedic day surgery. Therefore, not only optimizing pain at rest but also dynamic pain, pain during movement, is important for functional recovery. Locoregional analgesic techniques, as a component of multimodal analgesia, have long been used, but methods allowing early ambulation, at the same time offering adequate pain relief are under continuous investigations. The more complex surgery is performed on day basis, the more effective is pain management expected to be. Though e.g. neither transdermal fentanyl, 12 µg/h, nor ankle block reduced pain or opioid consumption after hallux valgus procedure (Turan et al. 2007), they may offer advantages after more complex and painful foot surgeries. Also for more demanding knee surgery the best pain modalities are being evaluated. Femoral block is one solution, but significant

motor weakness does occur, contrary to adductor canal block which spares motor function (Kwofie et al. 2013, Kim et al. 2014). Interesting experiments with local anaesthetics inducing sensory block without motor block have been published (Roberson et al. 2011). The peripheral blocks represent distinctively procedure-specific approach. Consequently, the method of choice in pain management depends on the surgical procedures performed in future day surgery.

Eventually, as stated about postoperative pain in an editorial by Mc Lean (Mc Lean 2013): “The unavoidable outcome of today can become the preventable outcome of tomorrow.”

7. SUMMARY AND CONCLUSIONS

The majority of the patients after shoulder arthroscopy and hallux valgus or rigidus surgery experience less pain than previously reported. After immediate postoperative phase, the pain scores at the used specific time points were recorded mild, and the worst pain after discharge until the 3rd or 4th postoperative day was moderate.

1. Unilateral spinal anaesthesia can be achieved with 5 mg hyperbaric bupivacaine and 15 µg of clonidine. Clonidine intensifies the block and reduces slightly the pain scores. It also prolongs the block and increases the need of vasopressors.
2. Subacromial bupivacaine infusion up to 10 mg/h is a safe method for postoperative pain after shoulder arthroscopy to selected patients. It offers more effective pain relief than placebo but this efficacy is probably clinically insignificant and hampered by technical issues. However, it can be considered as one option to selected patients needing tailored pain management.
3. Transdermal fentanyl, 12 µg/h, offers an easy and safe treatment option as a part of multimodal analgesia after shoulder arthroscopy in carefully selected patients after shoulder arthroscopy.
4. Transdermal fentanyl, 12 µg/h, did not reduce any further the need for rescue oxycodone or pain scores after hallux valgus or rigidus surgery. Multimodal analgesia, with regularly taken ibuprofen and paracetamol together with a single dose dexamethasone, offers good background analgesia after hallux valgus and rigidus surgery.

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A handwritten signature in black ink, appearing to read 'Rika Merivirta'. The signature is fluid and cursive, with the first name 'Rika' written in a larger, more prominent script than the last name 'Merivirta'.

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